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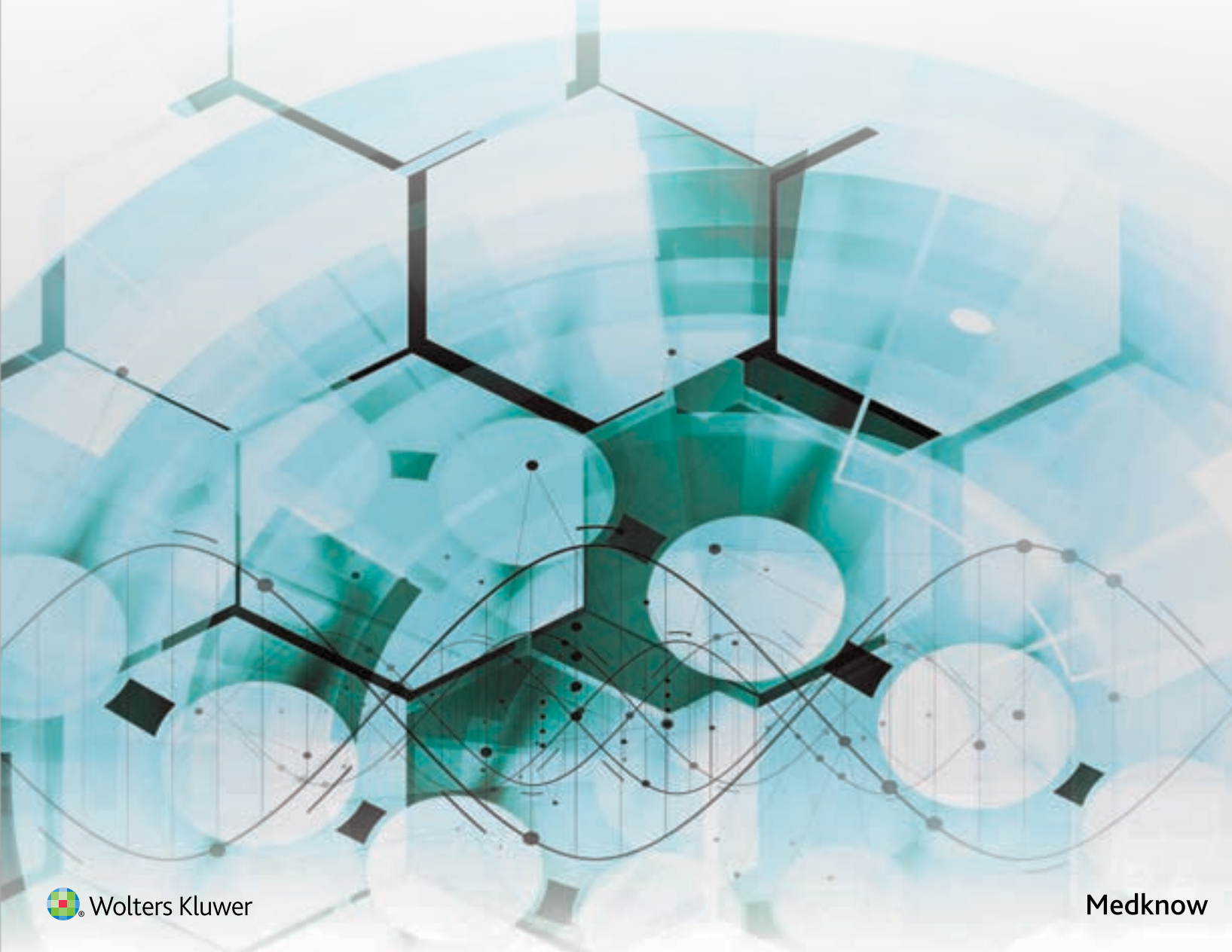

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CONTENTS

MicroRNA therapeutics: Dawning of a new era in precision medicine

Ever since the discovery of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), the central dogma of molecular biology has evolved to indicate the unidirectional flow of genetic information from DNA to messenger RNA (mRNA) to proteins. However, we are increasingly realizing that genetic information flow is much more complex than this. All cells carry the same complement of DNA and thus the same genetic information. Yet cells differentiate, proliferate, behave, and survive differently to make up different tissues and organs with their own specialized functions. It now appears that only about 74% of the genetic code is transcribed in humans. Of the transcribed component, only 2% is represented by mRNA that codes for proteins. These mRNA represent about 20,000 genes, though the number of proteins is much more than this arising through spice variants and further processing of large precursor proteins. However, the great majority, 98% of the transcriptome, is represented by non-coding RNA, of which there are various types.

MicroRNA (miRNAs) are a class of noncoding RNA that play a crucial role in cell differentiation, proliferation, and survival by binding to complementary target mRNAs, leading to mRNA translational inhibition or mRNA degradation. The first miRNA was identified in 1993 as a small RNA transcribed from the lin-4 locus of *Caenorhabditis elegans*, a tiny free-living soil nematode. The primary work was done in the laboratories of US researchers Victor Ambros and Gary Ruvkun establishing the astonishing facts that the lin-4 gene does not encode a protein product but instead gives rise to a small RNA and that lin-14 protein synthesis is negatively regulated by lin-4 RNA. Subsequent sequence analysis shows the complementarity of lin-4 to the 3′-untranslated region of the lin-14 gene, revealing the first miRNA–mRNA interaction. In 2000, the first mammalian miRNA, let-7, was discovered. These two key events have opened a Pandora's box revealing extensive transcription of many miRNAs and other noncoding RNAs in mammalian and nonmammalian genomes.

miRNA regulation now appears to be a key events in the differentiation, proliferation, and survival of cells in diverse tissues. Although miRNAs generally repress gene expression, a few miRNAs have also been detected that can upregulate genes. More than 3000 miRNA sequences have been identified and miRNA regulation is estimated to influence over 60% of human gene expression. Not surprisingly, the initial concept of miRNAs as developmental regulators has now substantially expanded, and miRNAs are now found to be dysregulated in numerous human diseases, including viral hepatitis, cardiovascular diseases, neurodegeneration, diabetes, autoimmune disorders, sepsis, myeloproliferative disorders, thalassemia, and many cancers. Moreover, miRNAs are frequently altered in disease states owing to genomic events, such as mutations, deletions, amplification, or transcriptional changes, or to biogenesis defects due to mutations or the downregulation of enzymes that regulate miRNA biogenesis. Tremendous interest has been aroused in utilizing specific miRNAs or miRNA families as biomarkers for disease diagnosis and prognostication and utilizing miRNA mimetics and inhibitors as therapeutic strategies.

The 2024 Nobel Prize in Medicine, awarded to the two pioneers who discovered miRNA and their function, thus heralds the dawn of a new era in precision medicine promising to change the diagnostic and therapeutic landscape of several diseases that cannot be treated adequately through conventional strategies.

Several strategies in miRNA therapeutics are being explored. These can be categorized into two main approaches based on the mechanisms of action: miRNA enhancement or replacement approaches that functionally increase and restore the expression of specific miRNAs, and miRNA inhibition to block the action of specific miRNAs. The former category includes miRNA constructs that may be delivered through nanoparticle carriers or recombinant viral vectors encoding miRNA sequences. The latter comprises anti-miR oligonucleotides (antagomirs or AMOs), miRNA masks, miRNA sponges, and miRNA decoys.

The design of efficient systems to deliver miRNA therapeutics to the target tissues remains a major challenge for the clinical application of miRNA-based therapies. The ideal delivery method should overcome

miRNA early degradation in the blood and poor tissue penetration while minimizing the risk of immunotoxicity and undesired off-target effects. Chemical modifications of the sugar ring or 3′-end have significantly improved miRNA stability against intracellular nucleases. Currently, miRNA therapeutics involve delivery through viral vectors, such as retroviral, lentiviral, adenoviral, and adeno-associated viral vectors, and nonviral-based systems, which include various types of nanoparticle organic and inorganic carriers.

There are several pointers to miRNAs becoming a successful new class of drug targets. Their small size and known and conserved sequence make them attractive candidates from a development standpoint. Many oligonucleotide-based gain- and loss-of-function studies have shown pronounced effects in rodents and even large animal models. The direct downstream targets of a single miRNA are commonly involved in signaling cascades. This implies that targeting a single miRNA probably will result in a dramatic effect due to the combinatorial effect of gene expression changes in all these related downstream targets. Progress in nanoparticle delivery systems coupled with lessons learned from antisense DNA technologies, have propelled us into oligonucleotide chemistries that can be applied to target miRNAs, developing antagomirs with remarkable affinity and specificity to qualify as drug candidates, both for common multifactorial conditions, as well as rare genetic disorders.

Yet, major challenges remain. The very fact that individual miRNAs can regulate a broad array of mRNA targets increases the likelihood of off-target effects that may reflect in unexpected adverse events. Several candidates have been discontinued in early-phase clinical trials owing to toxicity concerns, underscoring the need for comprehensive risk assessments of miRNA therapeutics. miRNAs are crucial in regulating gene expression during development, so their modulation in children requires careful assessment of potential impact on growth and development. Preclinical studies must rigorously evaluate these impacts to ensure safety. The developing immune systems of pediatric patients may also react differently to miRNA therapies compared to adults, necessitating delivery systems that minimize immune activation and enhance biocompatibility Additionally, the long-term effects of miRNA therapies are not understood and hence, even if licensed, long-term follow-up studies are essential to monitor for delayed adverse effects along with sustained efficacy. These issues bring up new ethical challenges. Finally, ensuring equitable access to these innovative treatments, regardless of socio-economic status, requires a collaborative approach involving researchers, clinicians, manufacturers, civil society, and regulatory bodies, to establish guidelines that ensure access as well as safety and well-being both during clinical trials as well as during clinical use.

Many biopharmaceutical companies and research institutions are investing resources in developing miRNA-based products and hundreds of patents are being filed. Most miRNA patents are related to cancer, metabolic disorders, and inflammatory disorders. Nevertheless, there is not yet s single miRNA-based therapy approved by the United States Food and Drug Administration or in an advanced phase of clinical trials. They are at present only in the preclinical or initial stages. Examples include cobomarsen (MRG-106) for the treatment of cutaneous T-cell lymphoma, mycosis fungoides subtype; and remlarsen (MRG-201), an miR-mimic to treat keloids. However, this is only the dawn and the day is breaking on a promising new era. Advances in bioinformatics and *in silico* drug design technology are developing fast to throw up new targets every day to be explored in a variety of disease processes.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Sex-related differences in cognition and its correlation with lipid parameters and sex steroids among community-dwelling older persons in Nigeria

Isyaku Gwarzo Mukhtar, Mohamed Mabrouk El-Khashab, Muhammad Ali Salim, Salisu Ahmed Ibrahim, Isyaku Umar Yarube

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Abstract

Introduction: Studies on sex-related differences in cognition and its correlation with serum lipids and sex steroids in older persons in sub-Saharan Africa (SSA) are few and inconsistent. Our objectives were to assess: (i) sex-related differences in cognition and (ii) the correlation of cognition with lipid parameters, age, years of formal education, and sex steroids in community-dwelling older persons in Kano state, Nigeria.

Materials and Methods: About 143 eligible participants were randomly selected. We used the Montreal Cognitive Assessment-Basic (MoCA-B), verbal fluency test, 10-Item Word List Learning Test (10-IWLLT), delayed word list recall, and Stick Design Test (SDT) to assess cognitive function. Serum lipids were determined using chemical colorimetry, whereas sex steroids were determined using competitive enzyme-linked immunosorbent assay kits.

Results: The results revealed that the participants had a mean age of 66 years. The mean MoCA-B score was 18.84 (males = 20.26, females = 17.73, $P = 0.001$). Males had better scores in orientation ($P = 0.001$), abstraction ($P = 0.009$), naming ($P = 0.001$), verbal fluency ($P = 0.013$), delayed word list recall score ($P = 0.001$), visuo-construction ($P = 0.015$), and visuo-perception ($P = 0.003$). Among whole participants, there was a positive correlation between total cholesterol and MoCA-B ($r = 0.236$, $P = 0.005$) and between low-density lipoprotein-cholesterol and MoCA-B ($r = 0.207$, $P = 0.013$). Serum testosterone had positive correlation with MoCA-B score (r = 0.212, $P = 0.001$) but negative correlation with delayed word list recall ($r = -0.218$, $P = 0.009$), and SDT ($r = -0.181$, $P = 0.031$); dihydrotestosterone had positive correlation with MoCA-B score ($r = 0.210$, $P = 0.012$) but negative correlation with delayed word list recall ($r = -0.243$, $P = 0.003$) and SDT ($r = -0.183$, $P = 0.028$). Estradiol had a negative correlation with the 10-IWLLT ($r = -0.169$, $P = 0.044$).

Conclusion: This study concludes that males had better cognition than females. Higher levels of serum lipids and sex steroids are related to better cognition in community-dwelling older persons in Nigeria.

Keywords: Cognition, older persons, serum lipids, sex steroids, sexual dimorphism

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INTRODUCTION

Several studies have reported sexual dimorphism in cognition.[1] Males are said to do better in spatial tasks, whereas females do better in verbal fluency and verbal memory.[1] Sexual dimorphism is also observed in some cognitive disorders; males with schizophrenia tend to present with severe cognitive impairment compared with females, whereas females are twice at risk of developing dementia compared with males.[2] These observations have led to increasing interest in the possible role of sex steroids in cognition and cognitive disorders. Testosterone receptors have indeed been reported in many brain areas responsible for learning and memory.[3] However, while biological pieces of evidence continue to accumulate concerning the neuroprotective effects of testosterone in both animal and human studies, results of testosterone supplementation trials have failed to produce consistent outcomes.[4,5] Furthermore, studies on the possible effects of sex steroids on cognition in older people in sub-Saharan Africa (SSA) are lacking.

Despite the reported link between dyslipidemia and dementia,[6] studies have continued to report inconsistent relationships between serum lipids and cognition in older persons.[7-9] Zhao *et al*.[9] found no significant relationship between lipid parameters and impairment in cognition but reported high total cholesterol (TC) to be positively correlated with measures of cognition in men and high low-density lipoprotein-cholesterol (LDL-c) to be positively so in women. Conversely, in a Swedish study,[8] higher serum triglycerides (TG) and high-density lipoprotein cholesterol (HDL-c) were found to be better predictors of verbal abilities and perceptual speed in women; however, serum lipid parameters were lesser predictors of cognitive trajectories in men.

Aims

This study aimed to assess sex-related differences in cognition and its correlation with serum lipids, age, education, and sex steroids in community-dwelling older persons in Kano, Nigeria.

Objectives

The objectives of this study are as follows:

(i) To assess sex-related differences in cognitive function in community-dwelling older persons in Kano, Nigeria.
(ii) To assess the correlation of cognition with serum lipids, age, years of formal education, and sex steroids in community-dwelling older persons in Kano, Nigeria.

MATERIALS AND METHODS

Participants selection and study design

The study was cross-sectional; it was carried out in three towns in Kano, Nigeria, between February 2020 and August 2023. The participants were healthy males and females aged 60 years and above who signed written informed consent and fell outside the exclusion criteria. A town crier was used to invite prospective participants by making announcements using the public address system on Friday and Saturday evenings to a central data collection point. Each prospective participant was initially screened for eligibility; those who were eligible were then prepared for data collection. This was done until the required sample size was obtained. A total of 179 persons turned up for possible participation. Thirty were excluded for failing to satisfy the inclusion criteria. Of the remaining 149, 6 were excluded for insufficient blood samples. Participants with known visual and or auditory impairment, neuropsychiatric disorders, diabetes, hypertension, renal impairment, history of stroke in the last 12 months, history of cigarette smoking, or history of alcohol consumption were not included in this study.

Ethical consideration

All participants signed written informed consent. Ethical clearance was obtained from the Kano State Research Ethics Committee (MOH/Off/797/T.I/1929, February 6, 2020).

Sample size determination

We used G*Power software (Universität Düsseldorf, Germany)[10] to compute sample size. Mean Montreal Cognitive Assessment (MoCA) scores of 25.32 ± 3.761 and 22.81 ± 4.659 for older men and women respectively,[11] were used which gave an effect size (d) of 0.59; $d = 0.59$, $\alpha = 0.05$, and statistical power of 0.8 were then used, giving a sample size of 46.

Assessment of cognition

We used a verbal fluency test to assess executive function. The participants were instructed to name as many domestic animals and words that start with the letter "*F*," each in 60 s. The test has been used in community-dwelling elderly in northern Nigeria.[12]

We used MoCA-B to assess cognition and some cognitive domains.[13] It is scored on a 0–30 scale. One point each was added to the score of participants who had less than 4 years of formal education (if the score is <30) or those considered illiterate, that is, inability to read or write fluently. Episodic memory was determined using the 10-Item Word List Learning Task.[14] Participants were scored from 0 to 30, a score of 9 or lower was taken as an impairment in episodic

memory. Visuo-constructional abilities were assessed using the Stick Design Test (SDT).[15] Participants were scored from 0 to 12 with a score below 5 denoting impairment in cognition. The test has been used in community-dwelling older people in Nigeria.[12]. Word List Recall was used to assess working memory. Participants were scored from 0 to 10; a score of 3 or less was used as an impairment in working memory. A cognitive assessment was performed by two trained physiologists and one medical doctor. The medical doctor has previous experience in administering cognitive assessment tools and, therefore, supervises the whole process.

Determination of serum lipids

Serum lipids were measured using the enzymatic method. The method involves using specific enzymes to hydrolyze TC and TG to give colored solutions. HDL-c, on the other hand, was determined by precipitating LDL-c and very low-density lipoproteins out of solution using phosphotungstic acid, in the presence of magnesium ions. This gave a colored solution, the absorbance of which was measured by a spectrophotometer at a wavelength of 560 nm. The final concentration of each lipid parameter was then calculated from the absorbance of the colored solutions and the associated concentration. The serum concentration of LDL-c was determined indirectly from concentrations of TC, HDL-c, and TG using the Friedewald formula.[16]

Determination of serum total testosterone, dihydrotestosterone, and estradiol

Five mL of blood sample was drawn from the participants between 8 and 9:30 AM after an overnight fast, centrifuged at about 1000*g* for 10 min, and serum extracted and kept at –20°C. Serum sex steroids were assessed using competitive enzyme-linked immunosorbent assay (ELISA) kits from CALBIOTECH (El Cajon, CA, USA) and Elabscience (Houston, TX, USA), based on the manufacturer's instructions. The testosterone ELISA kit has a detection rate of 0.25–100 pg/mL, sensitivity of 1.16 pg/mL, and within and between assay coefficients of variation (CV) of 3.72% and 6.90%, respectively, whereas estradiol has a detection rate of 10–1000 pg/mL, sensitivity of 8.7 pg/mL, and within and between assay CV of 3.48% and 7.72%, respectively. The dihydrotestosterone (DHT) kit has a detection rate of 39.06–2500 pg/mL, sensitivity of 23.44 pg/mL, and within and between assay coefficients variability of less than 10%.

Data analysis

Statistical Package for Social Sciences, version 23.0 (IBM Corp., Chicago, IL, USA) was used in analyzing the data. Because the majority of the variables were skewed, logarithmic transformation was performed using natural logarithm. All statistical analyses were then performed on the log-normal variables and final results were obtained by back-transformation to the original scale of the respective variables. Student *t* test was used to determine the difference in quantitative variables. Pearson's correlation coefficient was determined to assess the correlation between quantitative variables and measures of cognitive function. *P* value ≤ 0.05 was used as the significance level.

RESULTS

The participants had a mean age of 65.69 years with females being older ($P = 0.003$). The participants had a mean MoCA-B score of 18.84 with the males having significantly better scores than the females (20.26 vs. 17.73, $P = 0.001$). Similarly, the male participants had better scores in orientation ($P = 0.001$), abstraction ($P = 0.009$), naming ($P = 0.001$), verbal fluency ($P = 0.013$), delayed word list recall ($P = 0.001$), visuo-constructional skills ($P = 0.015$), and visuo-perception ability ($P = 0.003$) [Table 1].

MoCA-B score had a negative correlation with age in all participants ($r = -0.605$, $P = 0.001$), among males ($r = -0.537$, $P = 0.001$), and females ($r = -0.617$, $P = 0.001$). Similarly, verbal fluency had a negative correlation with age in all participants ($r = -0.336$, $P = 0.001$), among males ($r = -0.366$, $P = 0.003$), and females ($r = -0.284$, $P = 0.012$) [Table 2a]. MoCA -Basic (MoCA-B) score had a positive correlation with years of formal education in all the participants ($r = 0.465$, $P = 0.001$) and among males ($r = 0.542$, $P = 0.001$) and female ($r = 0.239$, $P = 0.035$) participants. Equally, verbal fluency had a positive correlation with years of formal education in all the participants ($r = 0.223$, $P = 0.007$) but no correlation among male ($r = 0.171$, $P = 0.174$) and female ($r = 0.136$, $P = 0.234$) participants [Table 2b].

When the participants were considered as a single group, TC had a negative correlation with orientation ($r = -0.312$, $P = 0.001$), calculation ($r = -0.162$, $P = 0.050$), naming ($r = -0.256$, $P = 0.002$), and delayed word list recall ($r = -0.174$, $P = 0.038$) but positive correlation with MoCA-B ($r = 0.236$, $P = 0.005$). Serum TG also had a negative correlation with orientation ($r = -0.210$, $P = 0.012$), calculation ($r = -0.096$, $P = 0.025$), and naming ($r = -0.180$, $P = 0.031$) but positive correlation with verbal fluency ($r = 0.267$, $P = 0.001$). Serum LDL-c had a negative correlation with orientation ($r = 0.018$, $P = 0.001$) and naming ($r = -0.218$, $P = 0.009$) but a positive correlation with verbal fluency ($r = 0.286$, $P = 0.001$) and MoCA-B ($r = 0.207$, $P = 0.013$). Serum HDL-c was the least

Table 1: Age, number of years of formal education, and cognition

Variables	Males	Females	*t* statistic	Mean diff. (95% CI)	Total	*P* value
	Mean (SD)	Mean (SD)			Mean (SD)	
Age	63.86 ± 4.50	67.22 ± 8.12	−2.973	−3.36 (−5.59 to −1.12)	65.69 ± 8.12	0.003*
Years of education	5.40 ± 5.62	0.38 ± 1.76	2.66 ± 4.71	7.462	5.015 (3.687–6.344)	<0.000*
Orientation	5.531 (0.429)	4.892 (0.234)	−6.381	30 (22%–38%)	5.211 (0.381)	0.001*
Calculation	2.038 (0.480)	1.879 (0.563)	−0.881	7 (22%–90%)	1.953 (0.527)	0.380
Abstraction	2.345 (0.399)	2.052 (0.335)	−2.649	15 (4%–25%)	2.191 (0.373)	0.009*
Delayed recall	2.628 (0.429)	2.843 (0.481)	0.856	7 (8%–76%)	2.747 (0.458)	0.394
Naming	3.810 (0.346)	3.332 (0.506)	−4.564	29 (17%–38%)	3.569 (0.470)	0.001*
Verbal fluency	13.10 (0.336)	11.25 (0.380)	2.519	16 (3%–31%)	12.06 (0.367)	0.013*
Delayed word list recall	9.020 (0.640)	8.166 (0.672)	−3.245	30 (13%–44%)	8.592 (0.680)	0.001*
10-Item Word List Learning Test	8.94 (0.942)	8.07 (1.027)	−0.553	9 (30%–31%)	8.48 (0.987)	0.581
Stick Design Test	10.07 (0.778)	8.876 (0.854)	−2.472	29 (7%–46%)	9.468 (0.835)	0.015*
Visuo-perception	1.625 (0.438)	1.058 (0.422)	−2.970	19 (7%–30%)	1.331 (0.441)	0.003*
MoCA-B	20.26 (0.222)	17.73 (0.239)	3.429	14 (6%–23%)	18.84 (0.240)	0.001*

MoCA-B: Montreal Cognitive Assessment-Basic.
*Statistically significant variable

Table 2a: Correlation of age with measures of cognition

Age						
Variables	All		Males		Females	
	r	*P*	*r*	*P*	*r*	*P*
Fluency	0.405	0.001*	0.309	0.012*	0.463	0.001*
Orientation	0.281	0.001*	0.341	0.005*	0.136	0.235
Calculation	0.453	0.001*	0.267	0.032*	0.534	0.001*
Abstraction	0.369	0.001*	0.278	0.025*	0.401	0.001*
Delayed recall	0.316	0.001*	0.342	0.005*	0.357	0.001*
Naming	0.332	0.001*	0.228	0.068	0.285	0.011*
VF	−0.336	0.001*	−0.366	0.003*	−0.284	0.012*
DWLR	0.362	0.001*	0.446	0.001*	0.276	0.014*
10-IWLLT	0.072	0.390	0.223	0.074	−0.002	0.986
SDT	0.292	0.001*	0.345	0.005*	0.227	0.046*
VP	0.391	0.001*	0.39	0.001*	0.357	0.001*
MoCA-B	−0.605	0.001*	−0.537	0.001*	−0.617	0.001*

*Statistically significant correlation

Table 2b: Correlation of years of formal education with measures of cognition

Variables	All		Males		Females	
	r	*P*	*r*	*P*	*r*	*P*
Fluency	−0.147	0.079	−0.127	0.313	−0.217	0.057
Orientation	−0.581	0.001*	−0.498	0.001*	−0.223	0.050*
Calculation	−0.237	0.004*	−0.361	0.003*	−0.094	0.412
Abstraction	−0.383	0.001*	−0.394	0.001*	−0.227	0.046*
Delayed recall	−0.150	0.074	0.373	0.002*	−0.001	0.992
Naming	−0.340	0.001*	−0.293	0.018*	−0.153	0.180
VF	0.223	0.007*	0.171	0.174	0.136	0.234
DWLR	−0.349	0.001*	−0.328	0.008*	−0.212	0.062
10-IWLLT	−0.177	0.034*	−0.271	0.029*	−0.063	0.567
SDT	−0.338	0.001*	−0.369	0.002*	−0.216	0.058
VP	−0.432	0.001*	−0.463	0.001*	−0.287	0.011*
MoCA-B	0.465	0.001*	0.542	0.001*	0.239	0.035*

VF: verbal fluency, DWLR: delayed word list recall, 10-IWLLT: 10-Item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception, MoCA-B: Montreal Cognitive Assessment-Basic.
*Statistically significant variable

correlated with measures of cognitive function correlating only with calculation negatively ($r = -0.055$, $P = 0.050$) [Tables 3 and 4].

When the participants were considered separately based on sex, serum lipids had a positive and negative correlation with verbal fluency and orientation, respectively, among male participants. Serum lipids were similarly positively correlated with verbal fluency among female participants [Tables 5 and 6].

Serum total testosterone had a positive correlation with global cognitive function ($r = 0.212$, $P = 0.001$) and verbal fluency ($r = 0.162$, $P = 0.050$) but a negative

Table 3: Mean serum lipid parameters and sex steroids of the participants

Variables	Male	Female	*T*	Mean diff.	Total	*P* value
	Mean (SD)	Mean (SD)	Statistic	(95% CI)	Mean (SD)	
Total cholesterol	163.15 (0.43)	137.41 (0.36)	2.59	18% (04%–35%)	148.56 (0.40)	0.011*
Triglyceride	48.97 (0.63)	44.26 (0.59)	0.99	11% (35%–90%)	46.34 (0.61)	0.325
HDL-c	45.95 (0.33)	41.80 (0.34)	1.66	10% (23%–98%)	43.64 (0.34)	0.098
LDL-c	96.49 (0.75)	79.36 (0.76)	1.76	22% (51%–98%)	86.71 (0.67)	0.080
T (nmol/L)	1.88 (1.29)	6.31 (0.56)	20.09	92% (74%–115%)	0.68 (0.73)	0.001*
E2 (pg/dL)	35.06 (1.11)	38.46 (1.12)	0.91	11% (8%–17%)	32.46 (1.07)	0.366
DHT (pg/dL)	108.87 (0.99)	258.68 (0.53)	15.90	49% (40%–60%)	52.9 (0.64)	0.001*

diff: difference, HDL-c: high-density lipoprotein, LDL-c: low-density lipoprotein, T: testosterone, E2: estradiol, DHT: dihydrotestosterone.
Note. All serum lipid parameters were measured in mg/dL.
*Statistically significant

Table 4: Correlation of serum lipid parameters and measures of cognitive function

Variables	Tchol		Trigly		HDL		LDL	
	r	*P*	*r*	*P*	*r*	P	*r*	*P*
Orientation	−0.312	0.001*	−0.210	0.012*	−0.114	0.171	−0.290	0.001*
Calculation	−0.162	0.050*	−0.096	0.025*	−0.055	0.050*	−0.132	0.115
Abstraction	−0.143	0.089	−0.072	0.391	−0.021	0.803	−0.125	0.136
DR	0.062	0.466	0.117	0.163	0.120	0.154	0.020	0.814
Naming	−0.256	0.002*	−0.180	0.031*	−0.122	0.147	−0.218	0.009*
VF	0.325	0.001*	0.267	0.001*	0.113	0.180	0.286	0.001*
DWLR	−0.174	0.038*	−0.072	0.395	−0.104	0.216	−0.148	0.078
10-IWLLT	−0.106	0.206	−0.161	0.055	−0.137	0.102	−0.036	0.669
SDT	−0.138	0.100	−**0**.138	0.102	−0.055	0.513	−0.090	0.283
MoCA-B	0.236	0.005*	0.134	0.111	0.049	0.558	0.207	0.013*
VP	−0.135	0.108	−0.116	0.169	0.081	0.338	−0.126	0.133

Tchol: total cholesterol, Trigly: triglyceride, DR: delayed recall, LDL-c: low-density lipoprotein, HDL-c: high-density lipoprotein, VF: verbal fluency, DWLR: delayed word list recall, 10-IWLL: 10-Item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception.
*Statistically significant

Table 5: Correlation of serum lipids and measures of cognitive function among male participants

Variables	Total cholesterol		Triglyceride		HDL-c		LDL-c	
	r	*P*	*r*	*P*	*r*	*P*	r	*P*
Orientation	−0.303	0.014*	-0.233	0.062	−0.036	0.777	-0.342	0.005*
Calculation	−0.184	0.142	−0.117	0.353	−0.010	0.937	−0.165	0.189
Abstraction	−0.047	0.711	0.063	0.617	0.127	0.313	−0.099	0.431
DR	−0.028	0.827	0.089	0.481	0.103	0.415	−0.070	0.581
Naming	−0.176	0.162	−0.155	0.218	0.022	0.864	−0.225	0.072
VF	0.257	0.038*	0.190	0.130	0.176	0.162	0.244	0.050*
DWLR	−0.070	0.579	0.048	0.705	−0.153	0.224	−0.079	0.534
10-IWLLT	−0.013	0.917	−0.083	0.511	−0.096	0.445	0.034	0.791
SDT	−0.034	0.790	−0.030	0.814	0.181	0.149	−0.062	0.622
MoCA-B	0.193	0.124	0.101	0.425	−0.034	0.786	0.219	0.079
VP	−0.193	0.124	−0.160	0.202	0.045	0.720	−0.155	0.217

DR: delayed recall, LDL-c: low-density lipoprotein, HDL-c: high-density lipoprotein, VF: verbal fluency, DWLR: delayed word list recall, 10-IWLLT: 10-Item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception.
*Statistically significant

correlation with orientation ($r = -0.365$, $P = 0.001$), abstraction ($r = -0.186$, $P = 0.026$), naming ($r = -0.323$, $P = 0.001$), delayed word list recall ($r = -0.218$, $P = 0.009$), SDT ($r = -0.181$, $P = 0.031$), and visuo-perception ($r = -0.274$, $P = 0.001$). Similarly, serum DHT had positive correlation with MoCA-B score ($r = 0.210$, $P = 0.012$) and delayed recall ($r = 0.166$, $P = 0.048$) but negative correlation with orientation ($r = -0.361$, $P = 0.001$), naming ($r = -0.268$, $P = 0.001$), delayed word list recall ($r = -0.243$, $P = 0.003$), visuo-perception ($r = -0.236$, $P = 0.005$), and SDT ($r = -0.183$, $P = 0.028$). However, estradiol did not correlate with measures of cognitive function except for a negative correlation with verbal fluency ($r = -0.165$, $P = 0.049$) and 10-Item Word List Learning Test (10-IWLLT; $r = -0.169$, $P = 0.044$) [Tables S1–S3]. When the participants were segregated based on sex, serum sex steroids did not correlate with cognition except for a negative correlation between serum testosterone and visuo-perception ($r = -0.220$, $P = 0.050$) and a positive correlation between serum DHT and delayed recall ($r = 0.357$, $P = 0.001$) among female participants.

Table 6: Correlation of serum lipid parameters and measures of cognitive function among female participants

Variable	Total cholesterol		Triglyceride		HDL-c		LDL-c	
	r	*P*	*r*	P	*r*	*P*	*r*	*P*
Orientation	−0.157	0.169	−0.152	0.185	−0.091	0.427	−0.085	0.458
Calculation	−0.126	0.272	−0.072	0.532	−0.069	0.547	−0.090	0.435
Abstraction	−0.165	0.148	−0.181	0.114	−0.104	0.363	−0.093	0.418
DR	0.115	0.317	0.130	0.255	0.117	0.306	0.086	0.455
Naming	−0.223	0.049	−0.172	0.132	−0.135	0.238	−0.161	0.159
VF	0.332	0.003*	0.310	0.006*	0.023	0.844	0.293	0.009*
DWLR	−0.178	0.118	−0.135	0.237	−0.007	0.951	−0.154	0.177
10 -WLLT	−0.178	0.118	−0.219	0.054	−0.159	0.164	−0.093	0.418
SDT	−0.160	0.162	−0.199	0.080	−0.182	0.111	−0.064	0.575
MoCA-B	0.187	0.101	0.129	0.261	0.046	0.690	0.136	0.235
VP	0.020	0.865	−0.043	0.710	0.181	0.112	−0.028	0.808

DR: delayed recall, LDL-c: low-density lipoprotein, HDL-c: high-density lipoprotein, VF: verbal fluency, DWLR: delayed word list recall, 10-IWLLT: 10-Item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception.
*Statistically significant

DISCUSSION

This study assessed sex-related differences in cognition and its correlation with serum lipids in community-dwelling older persons in Kano, Nigeria. Male participants had significantly higher MoCA-B scores compared with females. This could be because the female participants are older. Indeed, age was negatively correlated with MoCA-B score in both male and female participants. Aging is said to be associated with morphological and physiological changes in the brain, especially areas that control cognition and memory.[17] These age-related changes could, therefore, be the reasons for the observed poorer MoCA-B score among the female participants in this study. Similarly, male participants had better orientation, abstraction, naming, and visuo-perceptual scores. Generally, males are said to do better in spatial tasks, whereas females do better in verbal tasks.[18] The male participants in our study were indeed better than the females in motor and spatial skills (measured by the SDT) and visuo-perceptual ability; however, the participants did not differ in fluency test. These findings on better abstraction and visuospatial abilities among male participants compared with the females in this study are similar to what was reported in the HUNT study.[19] They found male participants to have better scores in visuospatial skills and abstraction; they, however, differed with the finding of our study on delayed recall in which females performed better than males in their study. The female participants in this study indeed had about 7% better scores in delayed recall compared with the males, but it was not statistically significant.

We used 10-IWLLT to assess episodic memory; delayed word list recall to assess working memory; verbal fluency to assess semantic memory and executive function; and SDT to assess visuo-constructional or spatial abilities. The mean scores for these tests were normal, except for the 10-item word list learning test and delayed word list recall, implying that the participants had impairment in episodic and working memory but normal semantic memory, executive function, and visuo-constructional ability. Some studies have reported age-related impairment in episodic memory among healthy community-dwelling older persons and among cognitively impaired patients.[20]

The participants in our study had fairly normal serum lipids. The finding of normal serum lipids in our participants is not surprising because the majority are rural dwellers who maintain a simple and active lifestyle and consume local food that is, low in fatty substances. Indeed, a similar normal metabolic profile has been reported among type 2 diabetics and non-diabetics in the same environment.[21] Of the four serum lipids studied, serum TC and LDL-c had a positive correlation with the MoCA-B score. This implies that an increase in serum levels of TC and LDL-c is related to better global cognitive function. A similar finding was reported by Zhao *et al*.[9] reported that high TC in males and high LDL-c in females have a positive correlation with cognition in elderly persons. Similarly, serum TC, LDL-c, and HDL-c were reported to be positively correlated with the digit substitution test, a measure of multi-domain cognitive function.[22] However, McFarlane *et al*.[7] reported significant differences in TC and LDL-c for different levels of cognition among normal, cognitively impaired, and dementia groups, in the PolSenior project. They found the highest concentrations of serum TC and LDL-c among the cognitively impaired group but the lowest concentrations among cognitively normal and mild dementia groups. We found no sex-related differences in correlation between serum lipids and MoCA-B score in our study even though some researchers,[23] found a sex-related association in baseline serum TC and LDL-c with 5-year cognitive decline. Serum TG and HDL-c did not correlate with MoCA-B in our study. This is similar to what has been reported by several authors.[7,22] TC, TG, and LDL-c had a negative correlation with naming, orientation, and calculation among

the participants as a single group, and with orientation among male participants. Conversely, TC, TG, and LDL-c were positively correlated with verbal fluency, a measure of semantic memory and executive function, among the participants as a single group, and among males and females. This suggests that higher serum lipids are associated with better executive function but poorer orientation, calculation, and naming skills, in both sexes. Taken together, serum lipids are associated with better global cognitive and executive functions but poorer orientation, calculation, and naming in our participants. This incongruent relationship of serum lipids with cognition or cognitive impairment has also been previously reported by researchers in the United Kingdom.[24] They found a weak relationship between serum LDL-c and impaired cognition or dementia in people 65 years and older but a stronger association in those younger than 65 years. The correlation of serum lipid parameters with cognition or cognitive impairment among older persons needs further clarification.

Our participants had low serum total testosterone. Aging is said to be associated with a gradual decline in serum testosterone.[5] The decline in serum testosterone is said to begin as early as the third decade of life and continues up to the ninth decade.[25] Therefore, our finding of low serum testosterone supports the general idea of a gradual decline in serum testosterone with aging. Total testosterone was positively correlated with MoCA-B score verbal fluency, implying that a higher level of serum total testosterone is related to better global cognitive and executive functions. This finding of a positive correlation of testosterone with global cognition and executive function is consistent with the growing number of pieces of literature supporting the possible role of testosterone on cognition. Indeed, studies have reported androgen receptors in brain areas responsible for cognition and memory in both human and non-human primates.[5,26] However, classical placebo-controlled, randomized, double-blind testosterone supplementation trials have continued to produce inconsistent outcomes.[4,27,28] This has raised questions about the true nature of the role of testosterone on cognition and memory and thus the possibility of interaction with other factors has been considered. One of such interactions could be hormone-hormone interaction. Testosterone is metabolized by 5α-reductase and aromatase to produce two active metabolites, DHT and estradiol. Despite the low testosterone level among our participants, the participants had normal serum estradiol and DHT. While serum estradiol did not correlate with any measure of cognitive function, serum DHT was positively correlated with MoCA-B score and verbal fluency. This suggests that higher serum DHT is associated with better global cognitive and executive functions.

While estradiol did not correlate with domain-specific cognitive measures, testosterone and DHT were positively correlated with verbal fluency. This implies that higher serum total testosterone or DHT is related to better executive function or semantic memory. In contrast, testosterone and DHT were negatively correlated with visuo-perception, visuo-constructional skills, naming, and orientation. This implies that higher serum total testosterone and DHT are associated with poor visuo-perception, visuo-constructional skills, naming, working memory, and orientation. However, neither testosterone nor DHT correlated with episodic memory. While disturbances in working, episodic, and semantic memory could be parts of the normal aging process, there are pieces of evidence for sex steroids-related impairment in memory function among older people.[29] Indeed, testosterone treatment has previously been reported to improve working memory in rats, in contrast to DHT.[30] The finding of this study on the positive correlation between testosterone and DHT with working memory is, therefore, consistent with what has been reported by other authors. However, the finding of no correlation between serum total testosterone and DHT with episodic memory contrasts those of other authors and should, therefore, be interpreted with context.

Limitations

Our study has provided data from an SSA on sex-related differences in cognition among community-dwelling older persons. We have also provided data on the relationship between cognition and serum lipids, age, formal education, and sex steroids upon which future studies can build. However, we could not match the participants for the level of formal education because of a limited number of females with formal education in this age group in the communities studied, this might have affected some of the findings of the study even though we used a cognition assessment tool that is, less sensitive to level of education. Similarly, the age difference between the male and female participants might have contributed to the sex-related difference in cognition we found.

CONCLUSIONS

Males outperformed females in global cognition, executive function, spatial and motor abilities, orientation, abstraction, naming, and working memory. Similarly, our findings suggest that serum lipids are related to better global cognition but poorer orientation, naming, and calculation skills;

furthermore, the higher the levels of testosterone and DHT, the better the global cognitive and executive functions in community-dwelling older persons in Kano, Nigeria.

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Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Table S1: Correlation of serum sex steroids and measures of cognitive function

Variable	T		E2		DHT	
	r	*P*	*r*	*P*	*r*	*P*
Orientation	−0.365	0.001*	0.041	0.631	−0.361	0.631
Calculation	−0.042	0.615	−0.062	0.463	−0.048	0.570
Abstraction	−0.186	0.026*	0.069	0.410	−0.159	0.058
DR	0.092	0.273	0.015	0.861	0.166	0.048
Naming	−0.323	0.001*	0.026	0.754	−0.268	0.001*
VF	0.162	0.050*	−0.165	0.049*	0.156	0.062
DWLR	−0.218	0.009*	−0.018	0.832	−0.243	0.003*
10-IWLLT	−0.066	0.434	−0.169	0.044*	−0.019	0.819
SDT	−0.181	0.031*	−0.043	0.611	−0.183	0.028*
MoCA-B	0.212	0.011*	−0.050	0.555	0.210	0012*
VP	−0.274	0.001*	0.039	0.644	−0.236	0.005*

DR: delayed recall, VF: verbal fluency, DWLR: delayed word list recall, 10-IWLLT: 10-Item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception, T: total testosterone, E2: estradiol, DHT: dihydrotestosterone.
*Statistically significant correlation

Table S2: Correlation of serum sex steroids and measures of cognitive function among male participants

Variables	T		E2		DHT	
	r	*P*	*r*	*P*	*r*	*P*
Orientation	0.053	0.674	0.033	0.795	0.003	0.983
Calculation	−0.104	0.411	−0.013	0.918	−0.121	0.337
Abstraction	−0.042	0.738	0.166	0.187	−0.200	0.110
DR	0.134	0.287	−0.122	0.332	−0.103	0.413
Naming	−0.038	0.762	0.039	0.761	−0.176	0.161
VF	−0.036	0.778	−0.147	0.244	0.260	0.037*
DWLR	0.096	0.446	−0.135	0.282	−0.110	0.383
10-IWLLT	−0.095	0.451	−0.206	0.100	0.000	0.998
SDT	−0.064	0.614	0.020	0.875	−0.205	0.101
MoCA-B	−0.069	0.583	−0.046	0.715	0.170	0.175
VP	0.000	0.998	0.006	0.962	−0.152	0.226

DR: delayed recall, VF: verbal fluency, DWLR: Delayed Word List Recall, 10-IWLLT: 10-item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception, T: total testosterone, E2: estradiol, DHT: dihydrotestosterone.
*Statistically significant correlation

Table S3: Correlation of serum sex steroids and measures of cognitive function among female participants

Variables	T		E2		DHT	
	r	*P*	*r*	*P*	*r*	*P*
Orientation	0.164	0.152	0.184	0.106	0.083	0.471
Calculation	0.121	0.291	−0.090	0.431	0.102	0.375
Abstraction	0.036	0.757	0.006	0.959	0.215	0.058
DR	0.018	0.873	0.115	0.318	0.357	0.001*
Naming	−0.025	0.827	0.072	0.531	0.135	0.239
VF	−0.031	0.789	−0.217	0.056	−0.186	0.102
DWLR	−0.030	0.793	0.120	0.297	−0.020	0.860
10-IWLLT	−0.026	0.823	−0.134	0.242	0.049	0.670
SDT	0.019	0.866	−0.067	0.558	0.074	0.521
MoCA-B	−0.047	0.682	−0.098	0.395	−0.144	0.207
VP	−0.220	0.050*	0.109	0.342	−0.015	0.896

DR: delayed recall, VF: verbal fluency, DWLR: delayed word list recall, 10-IWLLT: 10-Item Word List Learning Test, SDT: Stick Design Test, VP: visuo-perception, T: total testosterone, E2: estradiol, DHT: dihydrotestosterone.
*Statistically significant correlation

Original Article

Cognitive self-regulation as a predictor of social functioning in schizophrenia

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Abstract

Objectives: To explore the relation between cognitive self-regulation (CSR), social functioning, and psychopathology in schizophrenia.

Participants and Methods: About 100 patients diagnosed with schizophrenia according to ICD-10 were taken from the Department of Psychiatry of two Post-Graduate hospitals in Kolkata, India. Positive and Negative Syndrome Scale for Schizophrenia (PANSS), Schizophrenia Research Foundation India-Social Functioning Index (SCARF-SFI), and a specially designed questionnaire on CSR were administered.

Results: Results revealed that all the four subtests namely self-concern, occupational role, social role, and family role of the social functioning and symptoms scale of PANSS were significantly correlated with CSR.

Conclusion: CSR was found to be a highly reliable and valid tool and was able to predict social functioning along with positive and negative symptoms.

Keywords: Cognitive self-regulation, schizophrenia, social functioning

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BACKGROUND

Schizophrenia is a severe mental disorder characterized by a variety of signs and symptoms. Since the earliest descriptions of schizophrenia, impairments in social functioning contributing to poor quality of life were noted to be a rule rather than exception.[1,2] By definition, social impairments characterize schizophrenia, given that current diagnostic criteria require a disturbance or deficit in one or more major areas of functioning, such as work, interpersonal relations, or self-care.[3] Many studies have investigated the association between cognitive functioning and functional outcome, mostly with correlations or regression analyses.[4] Cognitive functions enable humans to perform in everyday life in the spheres of personal, social, and occupational activities. The ability to attend to things in a selective and focused way, to concentrate over a period of time, to learn new information and skills, to plan, to determine strategies for actions and to execute them, to comprehend language, and to use verbal skills for communication and self-expression, and to retain information and manipulate it to solve complex problems are examples of mental processes that are referred to as cognitive function. While almost all of these are taken for granted in most persons, they get impaired in schizophrenia. These impairments also affect the social functioning of the patients.[5]

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Most studies use a wide range of cognitive variables and outcome measures, some studies even use laboratory assessment of social skills as outcome measures. These studies in general find highly significant correlations showing the effect of cognition impairment on the functional outcome.[6,7]

In recent researches on schizophrenia, considerable attention has been paid to cognitive rehabilitation therapy. Researchers[8] observed that despite increased acceptance, the evidence base on its effectiveness is not impressive as the process is slow. Authors assumed that slow progress is due to several critical issues: (1) the importance of manipulating stimulus and context structure in rehabilitative interventions; (2) the need to base a cognitive rehabilitation of schizophrenia on cognitive neuroscience as opposed to neuropsychology; (3) the importance of systematically addressing motivation, self-esteem, and affective factors when designing cognition-enhancing interventions; (4) the need to move beyond one-size-fits-all interventions and develop individualized treatments; and (5) the need to address abnormalities in the experience of the self when designing interventions to optimize cognitive and behavioral performance. Besides the above factors, slow progress is due to less attention to different strategies of cognitive self-regulation (CSR) like selective attention to self and to others, planning, self-motivation to work, behavior regulation, and self-evaluation. These are important as cognitive abilities are impaired in schizophrenia in both positive and negative types.[9]

CSR assists individuals to integrate the learning process, consisting of the development of a set of constructive behaviors that affect one's use of cognitive abilities. These processes are planned and adapted to support the pursuit of personal goals in changing environments. It involves the control of various mental strategies for goal of better cognitive performance. It is the regulation of one's own thinking process and thus can fall in the domain of meta-cognition.[10] This study examined self-regulation of cognitive abilities as perceived by schizophrenic patients. This study examined the relationship between psychopathology, CSR, and social functioning in schizophrenia.

MATERIALS AND METHODS

Participants

About 100 patients diagnosed with schizophrenia according to ICD-10 were taken from the Department of Psychiatry of two Post-Graduate hospitals of Kolkata (West Bengal, India). All participants volunteered to take part in the study after giving written informed consent for participation. They were not having any active psychopathology and were taken from outpatient department (OPD) of the hospitals. Other inclusion criteria were (i) age ranged from 18 to 50 years and (ii) completed at least 7 years of full-time education (primary education). Exclusion criteria included (i) any comorbid psychiatric disorder, any neurological disorder, and significant medical condition, (ii) mental retardation or substance dependence except nicotine and caffeine, (iii) ECT in the last 6 months. Demographic characteristics of the sample are presented in Table 1.

Table 1. Sample characteristics (*N* = 100)

Variable	M	SD	Minimum	Maximum
Age	31.89	8.13	19	55
Illness duration (in years)	3.00	1.40	0.17	5
Variable	**Frequency**			**Percent**
Gender				
Female	26			26
Male	74			74
Employment status				
Employed	45			45
Unemployed	44			44
Others	11			11
Years in full-time education				
7–11	67			67
12–14	28			28
15–17	5			5
Diagnosis				
Paranoid	55			55
Undifferentiated	45			45

Instruments

(i) *Sociodemographic and clinical data sheet:* Semi-structured checklist used to record patient's sociodemographic particulars, along with clinical variables like diagnosis and duration of illness.

(ii) *Schizophrenia Research Foundation (SCARF) India-Social Functioning Index (SCARF-SFI):* This scale was developed by Padmavati, Thara, Srinivasan, and Shubha Kumar in 1995. This interview-based scale is intended for administration on persons suffering from psychiatric illnesses and the items are rated on a five-point scale, the higher the score, the better the social functioning. Social functioning is measured over 4 domains; they are self-concern (no. of items 4), occupational role (no. of items 4), role in the family (no. of items 4), and other social roles (no. of items 5) and maximum score possible for scale is 85. Information was obtained from the subject and/or informant and a global assessment of social functioning (GASF) score was computed GASF scores were categorized into three categories as per norms they was mild (GASF > 60), moderate (for range 30 to 60), and severe (GASF < 30).

(iii) *Positive and Negative Syndrome Scale for Schizophrenia (PANSS):* Developed by Kay *et al.*[11] is a 30-item scale (7 items for positive and negative symptoms each and

16 for general psychopathology) with 7-point rating categories ranged from absent (rating category = 1) to extreme (rating category = 7). The scale is used to assess the extent of severity on positive, negative symptoms and general psychopathology. A higher score represents a higher level of severity. It is specifically developed to assess individuals with schizophrenia and is used widely in research settings.

(iv) *Cognitive self-regulation questionnaire:* The CSR questionnaire for individuals with schizophrenia comprised of 10 items that require respondents to answer either "yes" or "no" was administered. The total score will be the total number of correct responses and will present the overall CSR. The CSR was administered as a pencil-and-paper measure, after initial rapport formation and detailed instructions given by the interviewer.

Questionnaire construction

The questionnaire was constructed after recording difficulties due to cognitive impairment faced by 15 patients diagnosed with schizophrenia and taking treatment from the out-patient of Psychiatry Department of Post-Graduation Hospital of Kolkata by means of semi-structured interviews and by taking opinions of experts who are in treating team of patients. Questions were framed upon the behavioral regulation required to deal with these difficulties. Based on these difficulties 20 items were framed and administered to 17 patients in psychiatric departments of hospitals and their feedback was taken to know whether they were able to understand the content of the questions or not. After necessary changes, and dropping of 4 irrelevant items the questionnaire with 16 items was sent to 3 experts (2 psychiatrists, 1 psychologist) for their feedback. They were asked to rate the items. After analyzing the rating of three independent experts and the author, 14 items were kept. Then the questionnaire was administered to 100 patients and the following psychometric properties were found.

Psychometric properties of CSR

The Kuder–Richardson coefficient of the responses to the CSR was found to be 0.76. However, 4 items with low item-total correlations with values less than 0.30 were dropped. The alpha for the remaining 10 items computed was found to be 0.82. The correlation coefficients between the cognitive function and CSR were as follows: attention (tested using Digit span, Trail Making A), which was found to be 0.55 and −0.32; verbal ability (tested using verbal fluency test semantic), which was found to be 0.67; mental flexibility (tested using Trail Making B), which was found to be −0.35; and stimulus inhibition (tested using the Stroop test), which was found to be −0.45. These results demonstrate a good concurrent validity.

Procedure

The present study took place at government-sponsored hospitals in the metropolitan city of Kolkata, situated in the eastern region of India. Initially, hospitals with psychiatric departments were approached with request to give permission to collect data from patients in Outpatient Department (OPD). Once the patient's diagnosis was confirmed by a psychiatrist, they were contacted for informed consent.100 out of 170 diagnosed patients gave informed consent. Then, initial rapport formed and necessary instructions were provided and the above-mentioned instruments were administered.

Statistical analysis

Data were analyzed using SPSS 16 version. Initially, the association between psychopathology, CSR, and social functioning was computed through the Pearson correlation coefficient, and then multiple regression was done to study variables that were able to predict social functioning in schizophrenia. The entry method was ENTER method for this regression analysis. In the first step, the variable that contributes the most to explaining the variance in social functioning is added to the model if it contributes significantly to the explanation of variance in social functioning for the model. This variable is typically selected based on a statistical criterion.

RESULTS

Descriptive statistics

Psychopathology

Sample mean rating on the PANSS was 2.62, (SD = 0.70) for positive symptom scale (Mean = 2.69, SD = 0.92), negative symptoms scale (Mean = 3.08, SD = 1.14) and for general psychopathology (Mean = 2.47, SD = 0.68) scores fall around mild level of severity.

Social functioning

Sample mean rating for SCARF–social functioning scale lies between rarely concerned to occasional lapses in concern level of function in different domains of social functioning that is, self-concern (Mean = 3.17, SD = 1.05), occupational role (Mean = 2.29, SD = 1.05), family role (Mean = 2.23, SD = 1.05), social role (Mean = 2.48, SD = 0.91) and overall score (Mean = 2.54, SD = 0.85).

Cognitive self-regulation

The sample mean for CSR questionnaire which consists of 10 questions and the response is in "yes" or "no" was 5.03 (SD = 3.12).

Correlation and regression

To examine the relationship between CSR, psychopathology, and social functioning, Pearson correlation coefficients were

Table 2: Inter-correlation matrix of Pearson correlation coefficients between cognitive self-regulation, psychopathology, and social functioning (*N* = 100)

Domains of CSR, PANSS & SCARF Social Functioning Scale	1	2	3	4	5	6	7	8	9
1. CSR	1								
2. PANSS (+)	−0.27**	1							
3. PANSS (−)	−0.53**	0.30**	1						
4. PANSS total	−0.52**	0.58**	0.85**	1					
5. Self-concern	0.64**	−0.35**	−0.51**	−0.51**	1				
6. Occupational role	0.63**	−0.35**	−0.55**	−0.49**	0.61**	1			
7. Family role	0.53**	−0.44**	−0.61**	−0.64**	0.52**	0.68**	1		
8. Social role	0.59**	−0.48**	−0.51**	−0.57**	0.50**	0.72**	0.66**	1	
9. Social functioning total	0.70**	−0.48**	−0.64**	−0.66**	0.78**	0.89**	0.85**	0.86**	1

computed as shown in Table 2. All the four subtests of social functioning were positively and significantly related to CSR. Total social functioning was also found to be significantly and positively correlated with CSR. This implies higher level of CSR is associated with the higher social functioning in the patient with schizophrenia and also associated with the higher levels of self-care, family roles, occupational roles, and social roles. In Table 2, the intercorrelation between CSR, psychopathology (PANSS +ve, PANSS −ve), and social functioning is shown. Here, we can see Social Functioning is negatively correlated with PANSS + ve (−0.48) and PANSS −ve is significantly negatively correlated with social functioning with a correlation coefficient of −.64. However, CSR was significantly positively correlated with social functioning with a value of 0.70.

Table 2 also shows significant negative correlation between four subscales of the social functioning scale with symptoms scales of PANSS. CSR also has significantly negative correlation with symptoms scales of PANSS. Table 3 shows the result of multiple regression with social functioning as a predicted variable, it shows CSR along with positive and negative symptoms was able to predict social functioning.

Table 3 shows the regression analysis where dependent variable is social functioning and independent variables are psychopathology (PANSS −ve symptoms and PANSS +ve symptoms) and CSR. Adjusted R^2 is 0.64. R^2 is 0.66. F value is 60.72 ($P < 0.000$). β value for PANSS −ve is −0.32 (significant). For PANSS +ve is 0.26 (significant) and β value for CSR is 0.46 (significant). Consider P value < 0.05 as a level of significance.

DISCUSSION

Previous studies have shown impairments in the deficits include difficulties in the ability to work, to engage in social relationships, to attend to self-care, and to participate in recreational and community activities in schizophrenia.[12]

Table 3: Regression for predicting social functioning from psychopathology and CSR

Variables	Beta	Sig.
PANSS (−)	−0.32	0.00
PANSS (+)	−0.26	0.00
Cognitive Self -Regulation	0.46	0.00

$R^2 = 0.66$, $F = 60.72$, $P < 0.000$

The present study shows the relation of regulation of one's own cognitive abilities with the social functioning in schizophrenia. The social functioning is measured along with the subtests of self-concern, occupational role, family role, and social role in this study.

The result does not show the higher level of CSR among the patients. The result also shows the sample mean for overall social functioning to be moderate in global assessment of functioning, as this score falls within the moderate functioning range. Moreover, the mean rating on the subscales of social functioning, social concern falls between average and good, whereas for occupational role, family role, and social roles it is between poor and average. It shows that patients were better in self-concern in comparison to the other domains of social functioning while the social roles were found to be most affected.

In our findings, it has been seen that CSR shares a significant positive relation with self-concern. For proper self-concern, a person needs to pay attention to their own personal belongings and take care of their own health by planning visits to the doctor, if faced with any health complications. They also need to take medicines properly, remembering the proper timing and right dosage. These all require cognitive abilities and thus CSR comes to play a significant role here.

Similarly, in order to carry out occupational roles, social roles, and family roles, individuals need to pay attention to the various information, remember them, and use them properly when required, this all involves a great deal

of cognitive abilities. For better performance in these roles, CSR can play a crucial role as this study's findings show a significant positive association between CSR and occupational role, social role, and family role. Higher the CSR higher is the individual functioning in occupational role, social role, and family role.

CSR was also found to share a significant positive correlation with overall social functioning. This relationship becomes more important in the condition of schizophrenia where social functioning is highly compromised[13] and where the association between the cognitive impairment and social functioning is high.[14] A number of intervention studies, primarily of cognitive remediation also have shown that some executive and memory improvements are associated with subsequent social functioning change.[15–19]

CSR was negatively correlated with PANSS negative symptom scale, positive symptom scale, and also with overall symptomlogy. Domains of social functioning were also significantly negatively correlated with PANSS negative symptom scale, positive symptom scale and also with overall symptomlogy. It simply implies that severe the symptoms will get, the more impaired a patient's social functioning will become. As the patient symptoms get more severe, he will have more impairment in carrying out functions of his self-concern, occupational role, family role, and social role.

In order to understand further the relationship between CSR, psychopathology, and social functioning, multiple regression was done with social functioning as a predicted variable. The total numbers of independent factors was 3 (PANSS +ve, PANSS −ve, and CSR) and dependent factor was social functioning. Results show that CSR along with positive symptoms and negative symptoms was able to predict social functioning with $R^2 = 0.66$, $F = 60.72$, $P < 0.000$.

The psychosocial rehabilitation focusing on the training in regulation strategies to control the behavior to be able to use cognitive abilities effectively can help patient to improve their social functioning. The training program based on Bandura's[20] model of health efficacy can be helpful in increasing the CSR. The training programme consists of strategies for s*elf-observation* of behavior, for example, what I do to remember the way when go to a new place? *Judgment*: what should be done in the above situation? (try to remember the landmarks etc.) *self-response*: at last some rewarding self-response should be given to oneself.

The training program to teach skills and strategies for CSR would also help in increasing the overall social functioning of the patient as the present study has shown a significant positive correlation between the CSR and social functioning.

CONCLUSION

From the present study, it could be concluded that CSR and social functioning are significantly associated. The CSR questionnaire apparently emerged to be a reliable and valid tool for assessing life meaningfulness among patients with schizophrenia.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Original Article

A mixed methods study on non-adherence to oral antidiabetic agents in type 2 diabetes mellitus patients: Unveiling the post-intervention outcomes

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Abstract

Background: Type 2 diabetes mellitus (DM) is a chronic metabolic disease. Despite available treatments, non-adherence to prescribed regimens remains a significant challenge, influenced by various factors.

Objective: This study aims to investigate the effectiveness of interventions targeting adherence to oral hypoglycemic agents (OHAs) in T2DM management while understanding the factors contributing to treatment failure and exploring strategies to improve medication adherence and overall disease management.

Materials and Methods: A mixed research design, integrating qualitative and quantitative methods, was applied in this study. In-depth interviews and focus group discussions were conducted among 327 patients with T2DM attending the medicine department of a tertiary medical college in Bihar for 3 years. Participants were individuals (>18 years) taking OHAs but experiencing symptoms despite treatment. Various intervention techniques were applied. Data analysis involved qualitative coding and categorization of interview transcripts.

Results: The study revealed significant insights into the demographic profile of patients with T2DM , with notable patterns in age, gender, educational status, and employment. Forgetfulness, economic concerns, fear of adverse effects, complexity of treatment plans, non-availability of medication, and preference for alternative treatments emerged as primary barriers to adherence. Interventions led to improved adherence and diabetes management for the majority of patients, with 203 (62%) showing signs of improvement post-intervention.

Conclusion: This study highlights the significance of understanding and addressing barriers to adherence in T2DM management. Despite limitations, the insights gained offer valuable directions for future research and interventions aimed at enhancing adherence and patient outcomes in T2DM treatment.

Keywords: Focus group discussion, intervention, non-adherence, oral hypoglycemic agents, qualitative study, type 2 diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease that results in high blood sugar levels. Type 2 diabetes mellitus (T2DM) arises from a complex interplay of genetic predisposition, environmental influences, and lifestyle factors. Central to its pathophysiology is insulin resistance, wherein target tissues become less responsive to insulin's actions, leading to impaired glucose uptake and utilization. Concurrently, pancreatic beta-cell dysfunction results in diminished insulin secretion, exacerbating hyperglycemia. Chronic hyperglycemia, in turn, contributes to the development of microvascular and macrovascular complications, including neuropathy, retinopathy, nephropathy, and cardiovascular disease, emphasizing the necessity for effective management.[1-4]

The prevalence of diabetes varies across regions, with significant impacts on healthcare systems and economies. This condition affects millions of individuals worldwide and poses significant health risks if not managed properly. The global burden of DM is cumulative, with an estimated 463 million adults affected worldwide in 2019. This number is expected to rise to 700 million by 2045 if current trends persist. T2DM constitutes most diabetes cases, accounting for approximately 90% of diagnoses.[5,6]

Management of T2DM aims to control blood sugar levels, reduce symptoms, prevent complications, and improve the quality of life for individuals with diabetes. Management strategies typically include lifestyle modifications, pharmacotherapy, and, in some cases, insulin therapy.[7-9] Among pharmacological options, oral hypoglycemic agents (OHAs) such as metformin, sulfonylureas, and DPP-4 inhibitors offer convenience and efficacy in controlling blood glucose levels.[10,11]

Despite the availability of treatment modalities, non-adherence to prescribed regimens remains a formidable obstacle in managing DM effectively. Psychosocial factors, socioeconomic status, health literacy, medication side effects, and healthcare system-related barriers further contribute to non-adherence, posing formidable challenges to achieving optimal outcomes in T2DM management. Additionally, interventions that involve healthcare professionals in counseling, barrier monitoring, and problem-solving can significantly improve medication adherence. The importance of interventions for non-adherence lies in their ability to enhance treatment effectiveness, reduce the risk of diabetes-related complications, and ultimately improve the quality of life for patients with diabetes mellitus.[12-14]

This study aims to provide valuable insights into the effectiveness of interventions on improving adherence to oral hypoglycemic agents in the management of diabetes mellitus and the objective of the study is to identify the factors of non-adherence to oral antidiabetics contributing to treatment failure and to find out the strategies to improve medication adherence and overall disease management.

MATERIALS AND METHODS

Study design

This study applied a mixed research design (both qualitative and quantitative), including in-depth interviews (IDI) and focus group discussions to recognize the causes of non-adherence to oral antidiabetic agents in the treatment of diabetes mellitus and analyze the post-intervention outcomes.

Study settings

The study was carried out at the medicine department of a tertiary medical institute in eastern India.

Study participants

The study participants were patients (>18 years) diagnosed with T2DM who were taking oral antidiabetic agents and attending the in-patient and out-patient medicine department of a tertiary medical institute in eastern India.

Number of participants

A total of 327 individuals, including 203 males and 124 females, with uncontrolled T2DM were included.

Inclusion criteria

The study included individuals with T2DM taking oral antidiabetic agents but still experiencing symptoms and gave their consent for in-depth interviews and focus group discussion.

Exclusion criteria

T2DM patients with co-morbid conditions were not included in the study. Twenty-six participants refused to participate in the study.

Study period

The research was done between April 2021 and March 2024.

Ethical considerations

Ethics committee approval was obtained from the concerned authority. Informed consent was obtained from all participants before participation, and confidentiality and anonymity were maintained throughout the study. Participants were assured of their right to withdraw from the study at any time without consequences.

Data collection

A total of 327 participants who consented to the study were involved in in-depth interviews and focus group discussions over 10–15 min, and 30–50 min each to collect the qualitative data. Field notes were taken while conducting the interviews. The interview was conducted in their language after explaining the study objective thoroughly.

Intervention

Healthcare professionals employed diverse intervention techniques to combat non-adherence to oral antidiabetic agents in diabetes treatment. Patient education and behavioral approaches, including reminder systems and motivational interviewing, encouraged consistent medication use, and technological aids like mobile apps aided in reminders and education, while provider-level interventions improved communication and engagement. Social support involving family and community health workers adopted adherence alongside personalized care plans applied to individual needs. Regular monitoring by healthcare professionals facilitated early identification of non-adherence, enabling timely intervention.[15-17] These strategies, informed by recent studies and reviews, encompassed educational interventions aimed at informing patients about diabetes management and medication importance.

Data analysis

The interview questions were open-ended. The text describes a research process where interviews were transcribed into English and manually studied. Descriptive "codes" were created from the textual data, and related codes were combined into "categories." The research adhered to the requirements for reporting qualitative research using consolidated criteria. The authors wrote, edited, and revised the script. Microsoft Excel was used to analyze the quantitative data.

RESULTS AND ANALYSIS

We have involved a total of 327 patients with T2DM through in-depth interviews and focus group discussions in our study period. The age group of patients varied from 18 to 85 years. The age-wise distribution of patients in the study is depicted in Table 1. The educational status of the patients with T2DM in the study is depicted in Figure 1.

The distribution of T2DM patients in the study reveals noteworthy patterns when categorized by age and

Table 1: Age-wise distribution of type 2 diabetes mellitus patients in the study

Age (years)	Male (203)	Percentage (%)	Female (124)	Percentage (%)	Total (327)	Percentage(%)
18–30	2	1	1	0	3	1
31–40	36	11	17	5	53	16
41–50	58	18	37	11	95	29
51–60	76	23	53	16	129	**39**
61–85	31	9	16	5	47	14

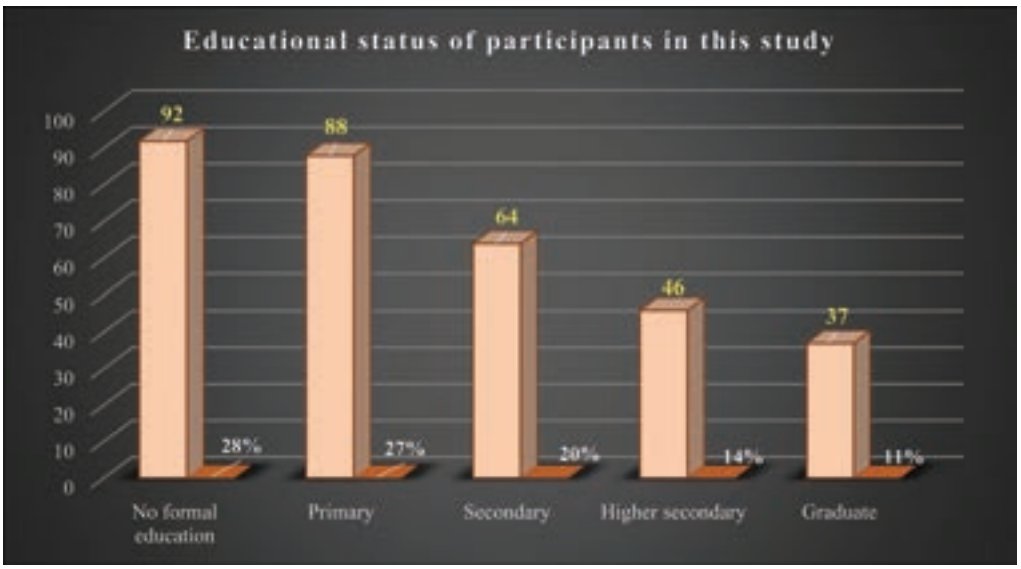

Figure 1: Educational status of type 2 diabetes mellitus patients in the study

gender. Among the age groups surveyed, the highest number of patients is observed in the 51–60 years of age group, constituting 39% of the total study population. In contrast, the lowest percentage is found among individuals of 18–30 years age group (1%). Across all age groups, males (62%) consistently exhibit higher representation compared to females (38%). This data underlines the importance of age and gender considerations in understanding the prevalence of T2DM within populations.

The educational status of T2DM patients, as indicated by the data from the study, demonstrates varied levels of educational attainment among the participants [Figure 2]. The largest proportion of patients possess those who had no formal education, accounting for 28% of the total. Following closely behind are those with primary education, comprising 27% of the patient population. Secondary education represents 20% of patients, while higher secondary education accounts for 14%. A smaller yet notable portion of patients are graduates, constituting 11% of the studied population. The study examined the employment statuses of patients with T2DM, revealing a diverse distribution within the studied population [Figure 2]. Among the categories observed, self-employment emerged as the most prevalent, with 160 (49%) of individuals falling into this group. Following closely behind were the unemployed individuals, constituting 88 (27%) of the population, while those who were employed comprised 52 (16%). Retired individuals accounted for the smallest proportion at 26 (8%). This breakdown sheds light on the occupational and educational landscape of patients with T2DM, indicating the importance of considering the background of the patients when addressing T2DM and developing appropriate interventions for affected individuals.

Figure 3 depicts a qualitative breakdown of the reasons behind non-adherence to T2DM treatment. Based on the data, forgetfulness (23%) emerges as the primary cause of barriers to adherence to conventional treatment of diabetes mellitus, indicating that patients frequently

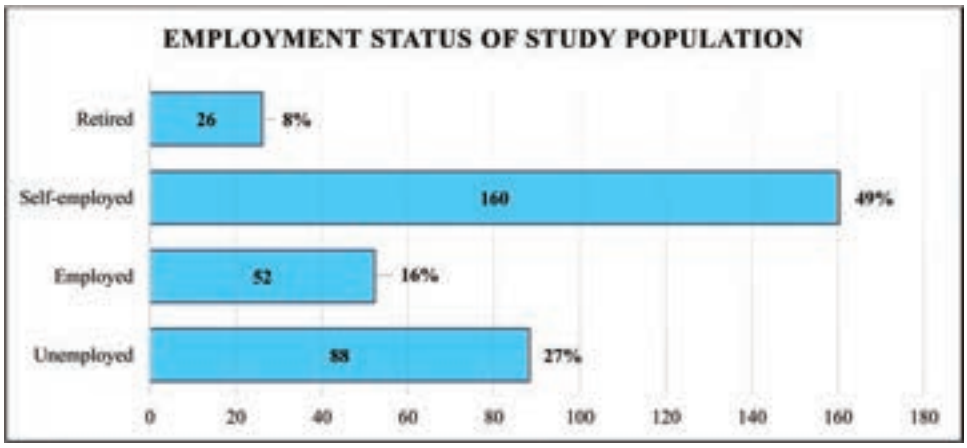

Figure 2: Employment status of patients with type 2 diabetes mellitus in the study

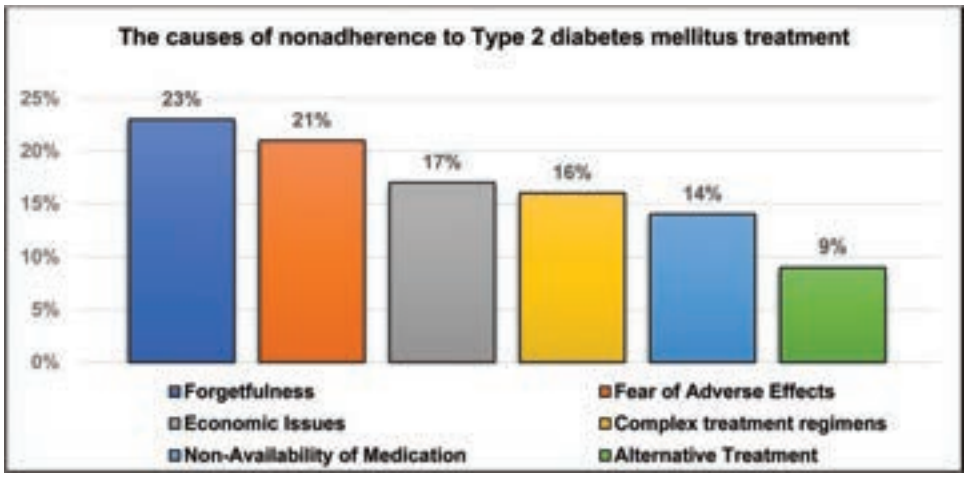

Figure 3: Qualitative data analysis of in-depth interviews of patients with type 2 diabetes mellitus regarding non-adherence to their treatment

overlook medication or treatment protocols. Economic concerns (21%) suggest that many patients struggle with treatment costs, leading to non-adherence. Fear of adverse effects (17%) discourages some patients from taking the treatment, while the complexity of treatment plans (16%) may overwhelm others, resulting in irregular intake of medicine. Non-availability of medication (14%) poses a significant barrier for some patients, while a minority (9%) express a preference for alternative treatments over the prescribed regimen. This analysis emphasizes the various array of challenges involved in managing T2DM, encompassing both personal factors such as forgetfulness and systemic issues like economic barriers and medication availability. It emphasizes the necessity for accessible treatment approaches to enhance adherence rates.

A range of intervention methods [Table 2] were employed to confront different obstacles hindering adherence and treatment efficacy as pinpointed in the research, ultimately enhancing results for individuals with T2DM.

Outcome after intervention

The implementation of intervention techniques in a study on non-adherence to conventional treatments in T2DM resulted in significant improvements. Patients became more adherent to treatment regimens, with increased awareness of medication importance and better diabetes management. Counseling sessions addressed psychological barriers, reducing forgetfulness and improving compliance. Detailed explanations from healthcare professionals alleviated concerns about medication side effects, and simplifying treatment regimens enhanced adherence. Collaboration with providers and pharmacies ensured consistent medication supply, and home delivery services improved access. Lifestyle adjustments and behavioral interventions promoted holistic diabetes management, leading to better glycemic control and overall well-being. These findings highlight the effectiveness of comprehensive approaches in addressing non-adherence in T2DM. As a result of the intervention, 203 (62%) showed signs of improvement. Conversely, there was no noticeable improvement in 36 (11%) patients, and 88 (27%) patients failed to attend subsequent follow-up appointments [Table 3 and Figure 4].

Table 2: Intervention techniques used for non-adherence to conventional treatments in type 2 diabetes mellitus treatment in this study

Category	Intervention techniques applied
Forgetfulness	•Healthcare providers employed various reminder systems such as smartphone apps, alarms, or pill organizers to help patients remember to take their medication.[17,18] •Education about the importance of proper intake of medicine and counseling to address underlying issues contributing to forgetfulness was provided, which proved beneficial [Table 3].
Fear of adverse effects	•Healthcare professionals offered detailed explanations about the potential side effects of medications, along with strategies to manage or mitigate them.
Economic issues	•Patients were informed about their options for affordable medications for diabetes. •The use of generic medications or alternative brands that were more affordable was encouraged.
Complex treatment regimens	•Healthcare professionals worked with patients to simplify treatment regimens by reducing the number of medications, adjusting dosing schedules, or using combination therapies when appropriate.[19]
Non-availability of medication	•Healthcare providers helped the patients in accessing medications through pharmacy services.
Alternative treatment	•Health professionals offered lifestyle adjustments, self-care recommendations, and behavioral interventions as alternative treatment options, focusing on holistic approaches to diabetes management.

DISCUSSION

The study involved 327 T2DM patients, aged between 18 and 85 years. The majority of patients were in the 51–60 years age group (39%) and were males (62%). The educational status varied, with the largest proportion having no formal education (28%), followed by those

Table 3: Distribution of type 2 diabetes mellitus patients after intervention (*n* = 327)

Patients' outcome after intervention	No. of patients	Percentage (%)
Did not turn up	88	27
No improvements	36	11
Improved	203	62

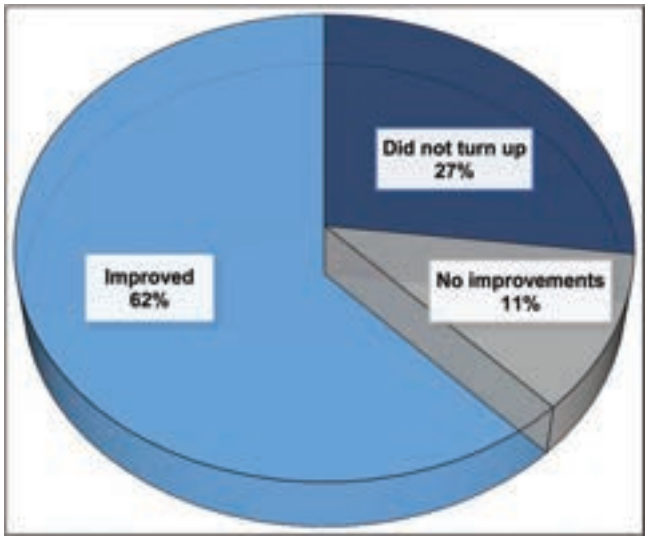

Figure 4: The outcome of intervention on type 2 diabetes mellitus patients

with primary education (27%). In terms of employment, self-employment was the most common (49%). The study identified several reasons for non-adherence to treatment, including forgetfulness (23%), economic concerns (21%), fear of adverse effects (17%), complexity of treatment plans (16%), non-availability of medication (14%), and preference for alternative treatments (9%).

Interventions were applied to address these issues, such as reminder systems and counseling for forgetfulness, detailed explanations about potential side effects, information about affordable medications, simplification of treatment regimens, assistance in accessing medications, and offering lifestyle adjustments and behavioral interventions as alternative treatment options. Post-intervention, 203 (62%) patients showed improvement, while 36 (11%) showed no noticeable improvement, and 88 (27%) failed to attend subsequent follow-up appointments. The interventions led to better diabetes management, improved adherence to treatment regimens, and overall well-being. The study highlights the effectiveness of comprehensive approaches in addressing non-adherence in type 2 diabetes.

This study highlights the importance of understanding the reasons for non-adherence to treatment in patients with T2DM and implementing targeted interventions to address these issues. The findings are consistent with previous studies that have identified similar barriers to adherence, such as forgetfulness, economic concerns, and fear of adverse effects.[20,21]

A study by Williams *et al.* involved a cohort of T2DM patients with a similar demographic profile, where interventions like reminder systems and counseling were implemented to address adherence barriers. This study reported comparable improvements in treatment adherence, with a significant proportion of patients demonstrating enhanced adherence and improved glycemic control post-intervention.[22] Brundisini *et al.* conducted a qualitative meta-synthesis of 86 empirical studies on barriers to medication adherence among T2DM patients. They identified seven categories of barriers, including emotional experiences, intentional non-compliance, patient-provider relationship and communication, information and knowledge, medication administration, social and cultural beliefs, and financial issues.[23]

Similarly, Torres-Robles *et al.* conducted a randomized controlled trial focusing on simplifying treatment regimens and providing detailed education on medication affordability. Their findings echoed the importance of such interventions in improving adherence rates among patients with T2DM, particularly among those with limited educational and economic resources.[24]

Another study by Lee *et al.* reported barriers to treatment adherence among patients with T2DM, including poor medical team performance, social dilemmas, and personal distress. These factors could potentially contribute to the non-availability of medication and preference for alternative treatments observed in your study.[25]

Moreover, some studies investigated the impact of behavioral interventions and lifestyle adjustments as alternative treatment options for T2DM patients facing adherence challenges. Their study demonstrated notable improvements in patient engagement and long-term adherence to treatment plans, affirming the holistic approach advocated in the present study.[26,27]

Significance of the study

This study highlights the significance of addressing non-adherence to oral antidiabetic agents in managing T2DM, emphasizing its global impact on patient health and healthcare systems. By unveiling the barriers to adherence, ranging from adverse effects to economic constraints, the study provides vital insights for healthcare providers to tailor interventions and support strategies, ultimately improving patient outcomes and reducing healthcare costs.

Limitations of the study

This study faces several limitations as its findings may not be universally applicable due to variations in demographics and healthcare systems. Methodological limitations such as small sample sizes and narrow focus on oral antidiabetic agents could bias results, and temporal constraints suggest insufficient tracking of long-term adherence patterns. These limitations indicate the need for further research to comprehensively understand medication adherence in T2DM.

Future perspective of the study

Future research could leverage insights from the study to develop targeted interventions, personalize treatment plans, and drive policy changes aimed at enhancing adherence and promoting patient-centered diabetes care.

By focusing on these aspects, the study can contribute meaningfully to the field of diabetes management and inform efforts to improve adherence rates and patient outcomes in T2DM treatment.

CONCLUSION

This study highlights the barriers to adherence, including forgetfulness, economic concerns, and fear of adverse effects. Interventions effectively addressed these issues, resulting in improved adherence and diabetes management for a majority of patients. This study can contribute meaningfully to the field of diabetes management and inform efforts to improve adherence rates and patient outcomes in T2DM treatment.

Acknowledgement

We are thankful to our study participants who have actively participated in this study throughout the study period.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Quality of life domains in patients with endocrine disorders: A study in the Al Jouf region of Saudi Arabia

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Abstract

Introduction: Data on the burden of endocrine disease in the Al Jouf region of Saudi Arabia are not available. This work aims to describe the burden of endocrinopathies in people.

Materials and Methods: Case files of endocrinopathy patients accessing care at a local district hospital located in the Al Jouf region of Saudi Arabia were extracted from the hospital database and appropriately analyzed.

Results: Records of 582 adult patients consisting of 184 (31.6%) males and 398 (68.4%) females were analyzed. Endocrine disorders recorded included diabetes mellitus (DM), thyroid disorders, hypothalamo-pituitary disorders, adrenal disorders, and gonadal disorders. All endocrine disorders predicted low quality of life (QoL), with DM having the highest odds (physical health: OR = 5.21, 95% CI = 2.23–10.42, $P = 0.001$; mental health domain: OR = 6.01, 95% CI = 2.71–13.79, $P = 0.001$; social relation domain: OR =4.27, 95% CI = 2.81–11.91, $P = 0.001$; environmental health domain: OR =5.01, 95% CI = 2.70–11.97, $P = 0.001$).

Conclusion: Endocrine disorders predicted low QoL, with DM having the highest odds across all four QoL domains.

Keywords: Burden, endocrine disease, impact

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INTRODUCTION

Quality of life (QoL) is multilevel and multifactorial in nature. It forms the eventual pathway shared by all physiological, environmental, and psychosocial mechanisms.[1] Endocrine disorders cause long-term morbidity associated with high mortality rates.[2] Diabetes mellitus (DM) negatively impacts QoL in Saudi adults, with retinopathy, DM foot disease, and neuropathy compounding this.[3] The significant burden of DM has a huge impact on the physical health and safety of patients.[4] The LEARNS (listen, establish, adopt, reinforce, name, and strengthen) model was developed to boost QoL in diabetes patients, and this yielded favorable outcomes in affected individuals.[5]

Alrudian *et al.*[6] found that individuals with primary hypothyroidism have low functional QoL values compared to non-diabetic participants. Alawaji *et al.*[7] showed significant relationships between hypothyroidism and

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the four QoL domains among study participants in Riyadh, Saudi Arabia. Al Quran *et al.*[8] also found that hypothyroidism patients on thyroxine replacement therapy had their QoL affected, irrespective of thyroid function test results. Vita *et al.*[9] showed that thyrotoxic patients, particularly those with Graves' disease, had worse QoL than euthyroidism patients. Chaves *et al.*[10] also showed that health-related QoL improved in all thyroid-related patient-reported outcome (ThyPRO) domains after surgery in patients with benign euthyroid goiter, while Alsaud *et al.*[11] showed that thyroid cancers affected QoL scores for functional domains.

Pituitary disease has a negative influence on QoL scores.[12] Although management of these disorders may improve the QoL, it is often still markedly reduced in individuals acromegaly with Cushing syndrome, despite treatment. This is further worsened by hypopituitarism, which often complicates pituitary surgery. Ho *et al.*[13] in a systematic review showed that QoL is reduced in adrenal disease patients, irrespective of adrenal function. Quality of life improved with treatment in persons affected with adrenal disorders, but was not completely reversed despite biochemical remission.

There are no available data on the impact of endocrine disorders on QoL in the Al Jouf region of Saudi Arabia. Hence, this study aimed to bridge this knowledge gap.

MATERIALS AND METHODS

The population size was calculated as shown below: [14]

$$\text{Minimum population size} = \frac{\text{Z-statistic}^2 \times P \times (1-P)}{d^2},$$

where Z is the statistic set at 95% confidence = 1.96; P is known prevalence of unfavorable QoL scores from the study by Al-Shehri[3] = 78.7%; d is the level of precision = 0.05.

Hence, the minimum sample population =

$$\frac{1.96^2 \times 0.79 \times 0.21}{0.05^2} = \frac{0.637}{0.0025}$$

= 255 (to the nearest whole).

This study was in line with good ethical standards[15] and included a review of the hospital records of endocrine patients managed in the daily adult endocrinology clinic of the Isawiyah General Hospital, located in the Isawiyah district of the Al Jouf region in Northern Saudi Arabia between October 2019 and June 2023. Isawiyah has a population of 5,000 consisting of Saudi nationals and non-Saudi residents.[16] The Isawiyah General Hospital is a 50-bed district hospital with a catchment of 50 km that accepts referrals from surrounding primary health centers.

Data were successfully extracted from the hospital's electronic health records (EHRs) using the research electronic data capture software, which is designed to support data extraction for research works.[17] Data collected included participants' personal identification data, patient diagnosis, and participants' response to the validated World Health Organization QoL Brief (WHOQoL-BREF) research questionnaire. WHOQoL-BREF assesses QoL domains with the aid of a system wherein response to each question is assessed on a 5-point Likert ordinal scale. The least score of 1 refers to very poor/very dissatisfied/none/never, while the highest score of 5 refers to very good/very satisfied/extremely/always.[18] A score of 2 and below is defined as low QoL in each domain. Every new patient in the clinic filled the WHOQoL-BREF questionnaire as part of their initial evaluation. Data from the filled questionnaires are subsequently entered into the EHR and saved in the hospital database.

These data obtained from the hospital records were further entered in a study protocol from where data were transferred to Microsoft Office Excel® 2010 for data management which involved verification of data, cleaning of verified data, appropriate handling of data with confidentiality, and use of codes to maintain participant anonymity, These were subsequently sent to SPSS version 21 (New York, NY, USA) for statistical analysis. Cronbach's alpha coefficient test statistic determined the reliability and internal consistency of the Arabic form of WHOQoL-BREF, while the confirmatory factor analysis (CFA) tested its validity.[19] An α-coefficient greater than 0.7 defined desirable questionnaire reliability. A statistically significant Bartlett's test of sphericity was needed for CFA testing. CFA was carried out with Kaiser–Meyer–Olkin (KMO) testing, with a KMO score greater than 0.6 indicating good validity of the questionnaire.

Mean (SD) described continuous variables, while *n* (%) described proportions. χ^2- and Fisher's exact tests determined the relationship between low QoL (the outcome variable) and independent categorical variables (age, sex, nationality, and endocrine disorders). Statistically significant risk factors were placed in a logistic regression to determine their odds of predicting QoL status. *P* value less than 0.05 defined statistical significance, while a difference of odds ratios (OR) greater than 1.22 defined clinical significance.[20]

RESULTS

To determine the validity and reliability of the QoL questionnaire, a pilot study involving 25 apparently healthy hospital workers was carried out, and α-coefficient values obtained were 0.825, 0.791, 0.762, 0.797, and 0.784 for the questionnaire, physical health domain, mental health domain, social interaction domain, and environmental health domain, respectively. The chi-square value of 5928.37 ($P = 0.0001$) obtained with the Bartlett's test of sphericity indicated good data suitability CFA testing. The KMO test score was 0.974. Hence, the WHOQOL-BREF (Arabic) questionnaire used for this study was both reliable and valid.

A total of 613 new patients presented to the diabetes and endocrinology clinic between October 2019 and June 2023, but 582 of them had complete data for analysis, and this was above the calculated minimum sample size of 255. Table 1 shows participants' social characteristics and demography. The subjects consisted of 184 (31.6%) males and 398 (68.4%) females with a mean (SD) age of 55.3 (6.3) years. Four hundred and three participants (69.2%) were Saudi nationals, while the remaining 179 (30.8%) persons were non-Saudi residents. Two hundred and eighty one (48.3%) participants had at least some education, while 397 (68.2%) participants had an estimated monthly earning of less than 5,000 Saudi riyals. Table 2 shows the distribution of endocrine disorders among study participants, with DM having the highest occurrence (70.6%), while gonadal disorders had the least occurrence (5.2%).

Three hundred and one study (51.7%) participants had low QoL in the physical health domain [Table 3], with a female preponderance [200(66.4%)]. Two hundred and one (66.4%) individuals were Saudi nationals, while the low QoL in this domain was slightly more in persons aged 65 years and above [160 (53.2%)]. Endocrine disorders were significant predictors of low QoL, with DM having the highest predicting odds, as shown in Table 3.

Table 4 shows interrelationships between study variables and mental health. Two hundred and eighty seven (49.3%) study participants had low QoL, with 201 (70%) females. One hundred and fifty seven (54.7%) persons with low QoL in the mental health domain were aged 65 years and above, while 209 (72.8%) Saudi nationals also had low QoL in this domain. Endocrine disorders predicted low QOL after adjusting for sociodemography characteristics, with DM having the highest odds (OR = 6.01, 95% CI OR: 2.71–13.79) of predicting low quality of life.

The social relation aspect of QoL was low in 306 (52.6%) study subjects [Table 5], of which 204 (66.7%) were females. Two hundred and one (65.7%) persons were Saudi nationals. Burden of diabetes mellitus was highest compared to other endocrinopathies after controlling for social and demographic factors (OR = 4.27, 95% CI OR: 2.81–11.91).

Of the 296 (50.9%) participants with low QoL in the environmental health domain, 173 (58.4%) were aged 65 years and above, while 199 (67.2%) were females. Two hundred and nine (67%) of these persons were Saudi nationals, and endocrine disorders significantly predicted

Table 1: Baseline characteristics of study participants

N = 582	
Study Variable	**Mean ± SD/*n* (%)**
Age (years)	55.3±6.3
Sex	
• Females	398 (68.4)
• Males	184 (31.6)
Nationality	
• Saudi nationals	403 (69.2)
• Non-Saudi residents	179 (30.8)
Education	
• No formal education	301 (51.7)
• Educated	281 (48.3)
Estimated monthly income (Saudi riyals)	
• <5000	397 (68.2)
• ≥5000	185 (31.8)

Table 2: Distribution of endocrine disorders among study participants

N = 582	
Endocrine disorders	***n* (%)**
DM	411 (70.6)
• T1DM	33 (5.7)
• T2DM	274 (47.1)
• GDM	102 (17.5)
•Other specific types of DM	2 (0.2)
Thyroid disorders	329 (56.5)
• Euthyroid goiter	74 (12.7)
• Thyrotoxicosis	54 (9.3)
• Hypothyroidism	201 (34.5)
H-P disorders	42 (7.2)
• Pituitary adenoma	29 (5.0)
• Prolactinoma	8 (1.4)
• Acromegaly	3 (0.5)
• Cranial DI	1 (0.2)
• Cushing disease	1(0.2)
Adrenal disorders	61 (10.5)
• Addison's disease	37 (6.4)
• CAH	9 (1.5)
• Adrenal tumors	15 (2.6)
Gonadal disorders	30 (5.2)
• Primary hypogonadism	12 (2.1)
• PCOS	15 (2.6)
• Gonadal tumors	3 (0.5)

CAH, congenital adrenal hyperplasia; DM, diabetes mellitus; DI, diabetes insipidus; GDM, gestational DM; H-P, hypothalamo-pituitary; PCOS, polycystic ovarian syndrome; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Table 3: Association of study variables with quality of life (physical health domain)

Study Variables	*N* = 582, *n* (%)		χ^2	*P* value	OR	95% CI OR
	Low QoL (physical health)					
	Present, *n* = 301 (51.7)	Absent, *n* = 281 (48.3)				
Age (years)						
• ≥65, *n* = 339 (58.2)	160 (53.2)	179 (63.7)	0.82	0.12		
• <65, *n* = 243 (41.8)	141 (46.8)	102 (36.3)				
Sex						
• Females, *n* = 398 (68.4)	Sex	198 (70.5)	0.98	0.93		
• Males, *n* = 184 (31.6)	101 (33.6)	83 (29.5)				
Nationality						
• Saudi, *n* = 403 (69.2)	201 (66.8)	202 (71.9)	0.52	0.81		
• Non-Saudi, *n* = 179 (30.8)	100 (33.2)	79 (28.1)				
Education						
• No formal education, *n* = 301 (51.7)	260 (86.4)	41 (14.6)	8.31	0.001	3.27	3.01–9.78
• Educated, *n* = 281 (48.3)	41 (13.6)	240 (85.4)				
Estimated monthly income (Saudi riyals)						
• <5000, *n* = 397 (68.2)	187 (62.1)	210 (74.7)	0.79	0.43		
• ≥5000, *n* = 185 (31.8)	114 (37.9)	71 (25.3)				
DM						
• Present, *n* = 411 (70.6)	279 (92.7)	132 (47)	9.21	0.001	5.21	2.23–10.42
• Absent, *n* = 171 (29.4)	22 (7.3)	149 (53)				
Thyroid disorders						
• Present, *n* = 329 (56.5)	240 (79.7)	89 (31.7)	7.32	0.01	2.04	1.53–8.59
• Absent, *n* = 253 (43.5)	61 (20.3)	192 (68.3)				
H-P disorders						
• Present, *n* = 42 (7.2)	32 (10.6)	10 (3.6)	5.79	0.001	3.13	1.27–9.46
• Absent, *n* = 540 (92.8)	269 (89.4)	271 (96.4)				
Adrenal disorders						
• Present, *n* = 61 (10.5)	42 (14)	19 (6.8)	5.49	0.001	2.71	1.29–9.24
• Absent, *n* = 521 (89.5)	259 (86)	262 (93.2)				
Gonadal disorders						
• Present, *n* = 30 (5.2)	23 (7.6)	7 (2.5)	3.84	0.001	2.96	1.13–8.27
• Absent, *n* = 552 (94.8)	278 (92.4)	274 (97.5)				

DM, diabetes mellitus; H-P, hypothalamo-pituitary; QoL, quality of life

Table 4: Association of Study Variables with Quality of Life (Mental Health Domain)

Study Variables	*N* = 582, *n* (%)		χ^2	*P* value	OR	95% CI OR
	Low QoL (mental health)					
	Present, *n* = 287 (49.3)	Absent, *n* = 295 (50.7)				
Age (years)						
• ≥65, *n* = 339 (58.2)	157 (54.7)	182 (61.6)	0.62	0.32		
• <65, *n* = 243 (41.8)	130 (45.3)	113 (38.4)				
Sex						
• Female, *n* = 398 (68.4)	201 (70)	197 (66.8)	0.56	0.28		
• Male, *n* = 184 (31.6)	86 (30)	98 (33.2)				
Nationality						
• Saudi, *n* = 403 (69.2)	209 (72.8)	194 (65.8)	0.29	0.57		
• Non-Saudi, *n* = 179 (30.8)	78 (27.2)	101 (34.2)				
Education						
• No formal education, *n* = 301 (51.7)	251 (87.5)	50 (16.9)	7.80	0.001	4.81	2.03–12.03
• Educated, *n* = 281 (48.3)	36 (12.5)	245 (83.1)				
Estimated monthly income (Saudi riyals)						
• <5000, *n* = 397 (68.2)	183 (63.8)	214 (72.5)	0.83	0.61		
• ≥5000, *n* = 185 (31.8)	104 (36.2)	81 (27.5)				
DM						
• Present, *n* = 411 (70.6)	262 (91.3)	149 (50.5)	12.61	0.001	6.01	2.71–13.79
• Absent, *n* = 171 (29.4)	25 (8.7)	146 (49.5)				
Thyroid disorders						
• Present, *n* = 329 (56.5)	207 (72.1)	122 (41.4)	8.32	0.01	2.73	1.82–9.18
• Absent, *n* = 253 (43.5)	80 (27.9)	173 (58.6)				
H-P disorders						
• Present, *n* = 42 (7.2)	35 (12.2)	7 (2.4)	10.2	0.001	3.85	2.03–9.22
• Absent, *n* = 540 (92.8)	252 (87.8)	288 (97.6)				
Adrenal disorders						
• Present, *n* = 61 (10.5)	43 (15)	18 (6.1)	10.9	0.001	3.11	2.16– 10.19
• Absent, *n* = 521 (89.5)	244 (85)	277 (93.9)				
Gonadal disorders						
• Present, *n* = 30 (5.2)	20 (7)	10 (3.4)	7.19	0.01	2.95	1.72–9.08
• Absent, *n* = 552 (94.8)	267 (93)	285 (96.6)				

DM, diabetes mellitus; H-P, hypothalamo-pituitary; QoL, quality of life

Table 5: Association of Study Variables with Quality of Life (Social Relation Domain)

Study Variables	*N* = 582, *n* (%)		χ^2	*P* value	OR	95% CI OR
	Low QoL (Social relations)					
	Present, *n* = 306 (52.6)	Absent, *n* = 276 (47.4)				
Age (years)						
• ≥65, *n* = 339 (58.2)	168 (54.8)	171 (62)	0.71	0.28		
• <65, *n* = 243 (41.8)	138 (45.2)	105 (38)				
Sex						
• Female, *n* = 398 (68.4)	204 (66.7)	194 (70.3)	0.19	0.47		
• Male, *n* = 184 (31.6)	102 (33.3)	82 (29.7)				
Nationality						
• Saudi, *n* = 403 (69.2)	201 (65.7)	202 (73.2)	0.58	0.22		
• Non-Saudi, *n* = 179 (30.8)	105 (34.3)	74 (26.8)				
Education						
• No formal education, *n* = 301 (51.7)	259 (84.6)	42 (15.2)	7.27	0.001	3.02	1.98–10.73
• Educated, *n* = 281 (48.3)	47 (15.4)	234 (84.8)				
Estimated monthly income (Saudi riyals)						
• <5000, *n* = 397 (68.2)	153 (50)	148 (53.6)	0.72	0.55		
• ≥5000, *n* = 185 (31.8)	153 (50)	128 (46.4)				
DM						
• Present, *n* = 411 (70.6)	288 (94.1)	123 (44.6)	9.71	0.001	4.27	2.81–11.91
• Absent, *n* = 171 (29.4)	18 (5.9)	153 (55.4)				
Thyroid disorders						
• Present, *n* = 329 (56.5)	214 (69.9)	115 (41.7)	8.11	0.01	2.46	1.74–9.13
• Absent, *n* = 253 (43.5)	92 (30.1)	161 (58.3)				
H-P disorders						
• Present, *n* = 42 (7.2)	32 (10.5)	10 (3.6)	10.7	0.001	3.01	1.32–10.66
• Absent, *n* = 540 (92.8)	274 (89.5)	266 (96.4)				
Adrenal disorders						
• Present, *n* = 61 (10.5)	47 (15.4)	14 (5.1)	9.4	0.001	2.83	1.49–9.07
• Absent, *n* = 521 (89.5)	259 (84.6)	262 (94.9)				
Gonadal disorders						
• Present, *n* = 30 (5.2)	19 (6.2)	11 (4)	7.1	0.01	2.91	1.52–11.15
• Absent, *n* = 552 (94.8)	287 (93.8)	265 (96)				

DM, diabetes mellitus; H-P, hypothalamo-pituitary; QoL, quality of life

low QoL after controlling for age, sex, monthly income, and nationality [Table 6]. Educational status was a significant predictor of low QoL in all four domains.

DISCUSSION

This retrospective study aimed to describe the burden of endocrine disorders in patients accessing care in a district hospital in Al Jouf, Saudi Arabia. The WHOQoL-100 is a health-related QoL tool formed following collaborations aimed at developing an instrument that will reflect the respondents' overall QoL as well as individual domains.[21] Pibernik–Okanovic found improved WHOQoL-100 scores in an intervention group of type 2 diabetes patients started on insulin compared to matched controls during the 2-month follow-up.[22] The WHOQoL-BREF questionnaire is an abridged instrument whose scores correlate with those of the WHOQoL-100.[21] The WHOQoL-BREF (Arabic version) showed appropriate internal consistency, reliability, and validity with an appropriate α-coefficient and KMO test values.

We found that 70.6% of the study participants selected for this study had diabetes mellitus, which significantly predicts low QoL across all four QoL domains. Al-Shehri *et al.* found that more than a fifth of diabetic patients had very low QoL values, with a female preponderance.[3] The gender difference was attributed to worse morbidity in female diabetics and the influence of gender inequality. Our study showed that sociodemographic factors did not predict QoL status, except for educational level. Audit of Diabetes Dependent Quality Of Life (ADDQoL) has been studied by various researchers and is a diabetes-specific questionnaire consisting of questions addressing two main items: 1. assessment of general QoL and 2. specific influence of DM on QoL status.[3,23] The WHOQoL-BREF unlike the ADDQoL has been shown to be relevant in both DM and other medical conditions. In our research work, gender was not a significant independent predictor of QoL status. This finding is supported by national data that show a bridge in the equality gap between males and females in Saudi Arabia due to the government's efforts in enhancing female rights in the Kingdom.[24]

The current study showed that thyroid disorders significantly predicted physical health (OR = 2.04, 95% CI of OR = 1.53–8.59; *P* = 0.01), mental health (OR=2.73, 95% CI of OR=1.82–9.18; *P* = 0.01), social relations (OR=2.46,

Table 6: Association of Variables with Quality of Life (Environmental Health Domain)

Study Variables	*N* = 582, *n* (%)		χ^2	*P* value	OR	95% CI OR
	Low QoL (Environmental Health)					
	Present, *n* = 296 (50.9)	Absent, *n* = 286 (49.1)				
Age (years)						
• >65, *n* = 339 (58.2)	173 (58.4)	166 (58)	0.63	0.27		
• <65, *n* = 243 (41.8)	123 (41.6)	120 (42)				
Sex						
• Female, *n* = 398 (68.4)	199 (67.2)	199 (69.6)	0.36	0.45		
• Male, *n* = 184 (31.6)	97 (32.8)	87 (30.4)				
Nationality						
• Saudi, *n* = 403 (69.2)	209 (67)	194 (71.9)	1.32	0.29		
• Non-Saudi, *n* = 179 (30.8)	103 (33)	76 (28.1)				
Education						
• No formal education, *n* = 301 (51.7)	231 (78)	70 (24.5)	6.08	0.001	3.88	2.06–9.79
• Educated, *n* = 281 (48.3)	65 (22)	216 (75.5)				
Estimated monthly income (Saudi riyals)						
• <5000, *n* = 397 (68.2)	169 (57.1)	228 (79.7)	0.92	0.13		
• ≥5000, *n* = 185 (31.8)	127 (42.9)	58 (20.3)				
DM						
• Present, *n* = 411 (70.6)	278 (93.9)	133 (46.5)	10.85	0.001	5.01	2.70–11.97
• Absent, *n* = 171 (29.4)	18 (6.1)	153 (53.5)				
Thyroid disorders						
• Present, *n* = 329 (56.5)	209 (70.6)	120 (42)	8.44	0.01	2.49	1.77–9.83
• Absent, *n* = 253 (43.5)	87 (29.4)	166 (58)				
H-P disorders						
• Present, *n* = 42 (7.2)	30 (10.1)	12 (4.2)	9.72	0.001	3.11	2.01–10.59
• Absent, *n* = 540 (92.8)	266 (89.9)	274 (95.8)				
Adrenal disorders						
• Present, *n* = 61 (10.5)	39 (13.2)	22 (7.69)	10.37	0.001	2.86	1.92–11.38
• Absent, *n* = 521 (89.5)	257 (86.8)	264 (92.3)				
Gonadal disorders						
• Present, *n* = 30 (5.2)	20 (6.8)	10 (3.5)	7.03	0.01	2.93	1.82–12.04
• Absent, *n* = 552 (94.8)	276 (93.2)	276 (96.5)				

DM, diabetes mellitus; H-P, hypothalamo-pituitary; QoL, quality of life

95% CI of OR=1.74–9.13; *P* = 0.01), and environmental health (OR=2.49, 95% CI of OR=1.77–9.83; *P* = 0.01) QoL domain scores. This finding is similar to those of previous reports showing the burden of thyroid disorders in affected patients. Thyroid malignancies cause about 836,000 disability-adjusted life years (DALYs), while iodine deficiency is the 85th main contributor to global DALYs, with Southern Asia and Sub-Saharan Africa being the most affected.[25] Studies carried out among Middle East residents with hypothyroidism showed low WHOQoL-BREF domain scores, although the predictiveness of QoL by hypothyroidism was not assessed in these previous works.[7,8]

Our study showed significant relationships between WHOQoL-BREF scores and other endocrine disorders such as hypothalamo-pituitary, adrenal, and gonadal disorders. This trend has been described by other research teams. Pituitary disorders place a significant burden on the clinical state of patients and an overall economic burden for healthcare systems. There is huge compromise in patients' QoL even after treatment, with disease sequelae requiring interventions that further affect quality of life.[26] Adrenal disorders are associated with decreased QoL scores, resulting in high morbidity and mortality rates.[27] Patients with adrenal insufficiency face enormous hospital costs and frequent hospital admissions. Gonadal disorders are associated with significant social and economic impacts.[28]

The major limitation of the current study is its retrospective approach and the use of an abbreviated version of the WHOQoL-100 questionnaire due to its cumbersome nature. However, the main strength of this research work is data provided on the burden of endocrine disease, especially in the Al Jouf region of Saudi Arabia, where such information is lacking.

CONCLUSION

This study shows significant associations between endocrine disorders that significantly predicted low QoL, with DM having the highest odds of predicting all four QoL domains compared to other endocrine disorders. The authors recommend future prospective and experimental research studies on this topic to shed more light on the burden of endocrine disorders in affected individuals.

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Author contributions

Drs. Chikezie Hart Onwukwe and Queen Henry-Okafor were involved in the conceptualization of the research topic. Dr. Chikezie Hart Onwukwe was involved in data extraction and wrote the various sections of the manuscript. Dr. Queen Henry-Okafor reviewed the analysis, writing, and editing.

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Conflicts of interest

There are no conflicts of interest.

Abbreviations

ADDQoL Audit of Diabetes Dependent Quality Of Life
CFA Confirmatory factor analysis
DALY Disability-adjusted life years
DM Diabetes mellitus
EHR Electronic health records
KMO Kaiser–Meyer–Olkin
LEARNS Listen, establish, adopt, reinforce, name, and strengthen
OR Odds ratio
QoL Quality of life
SD Standard deviation
ThyPRO Thyroid-related patient-reported outcome
WHOQoL-BREF World Health Organization quality of life brief

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Original Article

A randomized study to compare the efficacy and safety of ketamine, levobupivacaine, and a combination of both as pre-incision surgical site infiltration for providing postoperative analgesia in patients undergoing elective abdominal hysterectomy under general anesthesia

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Abstract

Objectives: We aimed to compare the postoperative Visual Analog Scale (VAS) score, requirement of additional analgesia, side-effects, and patient satisfaction among elective hysterectomy patients using ketamine, levobupivacaine, and a combination of both.

Materials and Methods: A comparative study was conducted on 60 adult females, randomly divided into three groups of Group K: ketamine 1 mg/kg in saline, 20 mL, Group L: levobupivacaine 0.25%, 20 mL, and Group KL: ketamine 1 mg/kg in 0.25% levobupivacaine, 20 mL. The study drug was infiltrated 5 minutes before skin incision. The patient outcomes (hemodynamic parameters, pain, requirement of additional analgesia, and side-effects) were observed during the 24 h after surgery and compared. $P < 0.05$ was taken for reference in terms of significant results.

Results: Group KL had the lowest pain VAS score at postoperative 1 h ($P = 0.022$), 2 h ($P = <0.001$), and 6 h ($P = 0.001$). The time of the first dose of pethidine requirement was longer and the cumulative pethidine requirement (24 h) was significantly less in group KL ($P < 0.001$). Nausea was present in six cases in group K, two cases of Group L, and none from group KL. The patient satisfaction score was significantly greater in group KL (3.30 ± 0.57) as compared to both groups K (1.90 ± 0.44) and L (2.50 ± 0.60), $P = 0.0001$.

Conclusion: The combination of ketamine and levobupivacaine is a safe and efficacious alternative as pre-emptive analgesia among patients undergoing abdominal hysterectomies. The combination enhances relief from postoperative pain and provides much better patient satisfaction.

Keywords: Analgesia, ketamine, levobupivacaine, pain, postoperative

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INTRODUCTION

Postoperative pain remains an important aspect for any surgery from the anesthetist's point of view since it may be associated with reduced quality of life, physiological alterations, and increased morbidity, resulting in delayed mobilization and resuming of normal daily activities.[1-3] An effective postoperative pain control is thus approached to provide better patient outcomes, comfort, and early discharge.[1-3]

Research on device methods to control postoperative pain has been carried out, which began in the form of systemically used opioids, i.v. analgesia, or epidural and spinal injections. Recently, there has been a localized wound infiltration with the local anesthetic,[4-6] which is a popular and safe technique for preventing wound pain. Pre-emptive analgesia before surgery prevents central sensitization of pain pathways and decreases analgesic requirements. The efficacy of different drugs such as bupivacaine, ropivacaine, levobupivacaine, ketamine, tramadol, and meperidine for preoperative surgical site wound infiltration for management of postoperative pain has been tested, with varied results.[7-10]

Among them, the use of opioids is common, and they are preferred for managing severe pain. Using opioid medications might cause adverse effects such as sedation, vomiting, nausea, and respiratory depression.[11] Besides opioids, bupivacaine is one of the commonest used anesthetic agents. It is a long-acting drug metabolized in the liver. It provides differential motor and sensory blockade and is an important choices for management of postoperative pain. Levobupivacaine is an S-enantiomer of bupivacaine, and it has shown equivalent efficacy, with a slightly superior safety profile in comparison to that of bupivacaine.[1,12]

Ketamine, on the other hand, is an antagonist of the NMDA receptor with substantial action on inhibiting C-fiber activity. Since the peripheral nerve endings have glutamate receptors that contribute to pain signaling, ketamine may be useful for providing pre-emptive analgesia, and along with that, side-effects of opioids, such as addiction, tolerance, or physical dependence, can be avoided. Ketamine also has a local analgesic effect.[8] Overall, the preoperative infiltration of these drugs may prolong the time for requirement of the first analgesia dose and decreased the total amount of the required analgesia dose.[1]

The pre-emptive analgesic efficacy of these drugs depends on the type of surgery, duration of surgery, patient age, and patient sensitivity to pain.[7] Hence, the choice of the analgesic drug and the method to gain maximum relief from postoperative pain remain of significant concern. Moreover, the combination of the anesthetic drugs holds importance as it may lead to a combination of mechanisms of action of both drugs with minimal side-effects of both drugs.

This study aimed to evaluate the safety and effectiveness of pre-incision surgical site infiltration using a combination of ketamine and levobupivacaine compared to the use of either drug alone in managing postoperative pain in patients undergoing abdominal hysterectomies, one of the most common gynecological procedures.

MATERIALS AND METHODS

A prospective, randomized, interventional, comparative study was conducted in the Anesthesia Department of a tertiary care hospital of New Delhi, from May 2019 to October 2019 after obtaining ethical clearance (IEC/VMMC/SJH/Thesis/October/2018-112, dated October 30, 2018).

The sampling population included women undergoing abdominal hysterectomies during the study period, with inclusion criteria of ASA I or II; age > 18 years; and duration of surgery for less than 2 h.

Any patient with drug allergies, cardiovascular disease (arrhythmia, congestive heart failure, hypertension, or coronary artery disease); psychiatric disorder; neurological disease, increased intracranial pressure, seizure, glaucoma, and hyperthyroidism; and liver or renal dysfunction as found during the routine pre-anesthetic checkup were excluded.

Sample size

Based on the study groups' cumulative 24-h pethidine requirements, the sample size was determined. In a previous study using a similar protocol, the 24-h pethidine requirement in patients receiving pre-incision levobupivacaine infiltration was 105.8 mg with an SD of 9.3.[1] With 90% study power, assuming 20% dropout rate, and 10% difference for cumulative pethidine requirement between the groups at an alpha level of 0.05, 20 cases per group were to be taken. Thus, for the study, 60 adult females who underwent elective abdominal hysterectomy under general anesthesia were enrolled (20 cases per group in three groups). Every patient provided a written, informed consent.

A total of 73 patients were considered for the study, out of which 13 were excluded as six did not meet inclusion

criteria and seven refused to participate. Sixty patients were randomized (through computer generated numbers) to receive either ketamine (Group K: ketamine 1 mg/kg in saline, total volume 20 mL) or levobupivacaine (Group L: levobupivacaine 0.25%, total volume 20 mL) or Group KL: ketamine 1 mg/kg in 0.25% levobupivacaine total volume 20 mL. There was no case of loss to follow-up [Figure 1].

Every patient provided a written, informed consent. All patients underwent a pre-anesthetic evaluation 1 day prior to surgery. After taking a detailed medical history and conducting a physical examination, the following details were documented: age, weight, and ASA grade. Necessary investigations were performed based on the patient's age and medical condition. Patients were instructed to fast for 6 hours before the procedure. As premedication, they were given 0.25 mg of alprazolam tablets the night before and on the morning of the surgery.

In the operating room, vital signs were monitored, and an 18-gage cannula was used for intravenous access. Anesthesia was induced with midazolam (1 mg), fentanyl (2 μg/kg), and propofol 10% (2 mg/kg), followed by vecuronium bromide (0.1 mg/kg) to facilitate ProSeal laryngeal mask airway (PLMA) insertion. The PLMA size was based on the patient's weight (Size 3 for 30–50 kg, Size 4 for 50–70 kg, and Size 5 for 70–100 kg). Anesthesia was maintained with oxygen and nitrous oxide (33:66 ratio) and isoflurane. A fentanyl bolus (1 μg/kg) was administered after 1 hour for analgesia.

Vital signs were recorded at various time points: during induction, PLMA insertion, drug infiltration, and every 15 min during surgery. Post-surgery monitoring continued in the PACU for 2 h. Patients were given 1 g of paracetamol every 8 h postoperatively. If the Visual Analog Scale (VAS) score reached 4 or higher, pethidine was administered, with additional doses if necessary. The

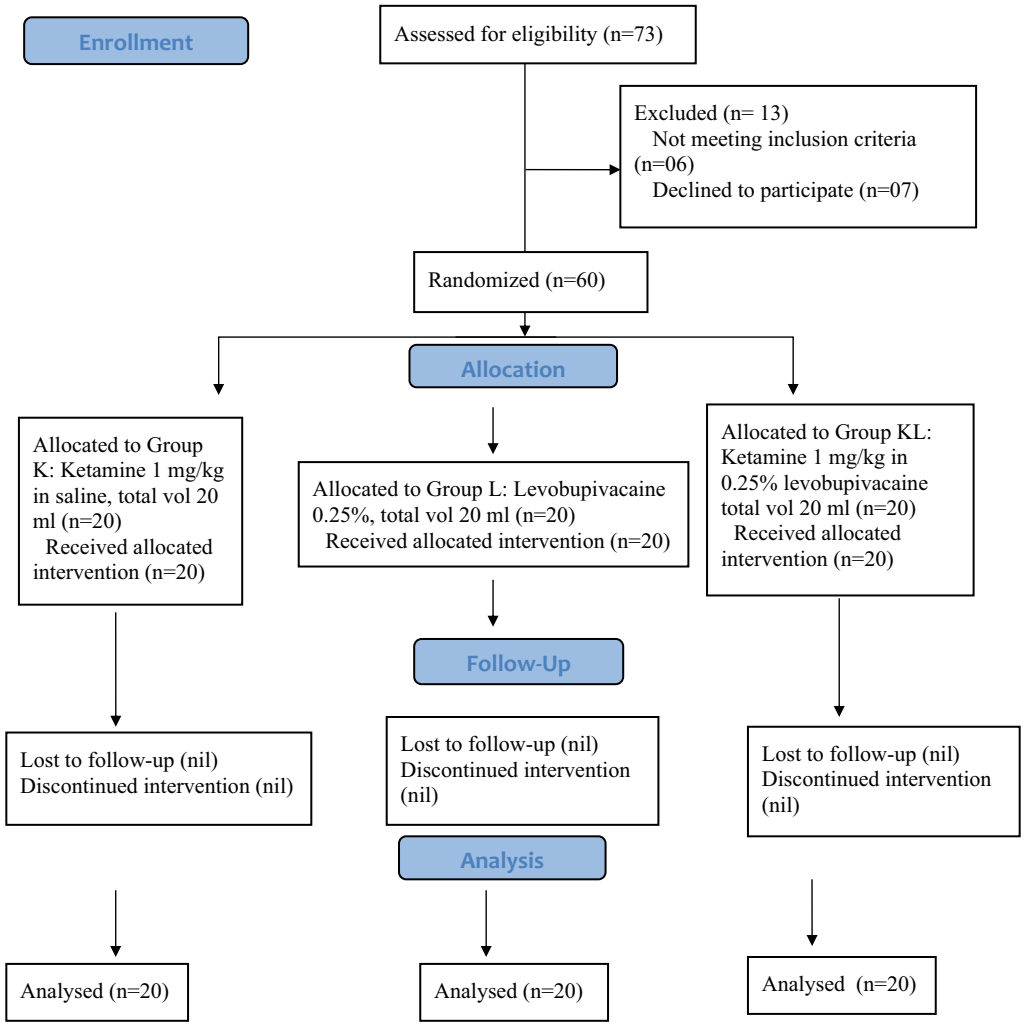

Figure 1: Consort flow

total pethidine consumption and time to the first dose were recorded.

Outcomes included pain severity (VAS score), sedation level, time to first pethidine dose, total pethidine use, side-effects (nausea, vomiting, sedation, and hallucinations), and patient satisfaction. Pain was rated on a 0–10 scale, nausea severity was graded, and sedation was assessed on a 4-point scale. Patient satisfaction was measured on a 5-point scale 24 h postoperatively.

Statistical analysis

Statistical analysis was performed using SPSS 16.0, with categorical variables analyzed using the chi-square test and continuous variables using one-way ANOVA. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the patient's details which were statistically comparable in the three groups. The patients' mean age in group K was 43.95 ± 4.11 years, in group L 45.65 ± 3.69 years, and in group KL 43.55 ± 4.71 years ($P = 0.25$), and the mean weight was 56.35 ± 10.00, 57.78 ± 9.77, and 54.38 ± 8.73 kg, respectively ($P = 0.52$). The mean surgery duration in groups K, L, and KL was 105.1 ± 7.12 min, 110.2 ± 5.10 min, and 111.4 ± 1.95 min, respectively ($P = 0.06$), and the mean of total fentanyl required intraoperatively was 169.05 ± 30.00, 173.40 ± 29.37, and 163.25 ± 26.32 (μg), respectively.

Overall, the VAS score was found to slowly increase from 0 to 24 h (postoperative period). Group comparison showed that group KL had the lowest VASA score against group K and group L at postoperative 1 h (2.2 ± 0.4 vs 2.7 ± 0.84 vs 2.25 ± 0.43, $P = 0.022$), 2 h (2.35 ± 0.57 vs 3.55 ± 0.97 vs 2.5 ± 0.59, p=<0.001), and 6 h (3 ± 0.63 vs 3.85 ± 0.85 vs 3.4 ± 0.49, $P = 0.001$) respectively. At postoperative 24 h, the VAS score was comparable among the three groups ($P = 0.575$). [Table 2]

The time required for the first dose of pethidine was significantly more in group KL compared to group K and group L (363.25 ± 8.1 vs 32.5 ± 4.61 vs 119 ± 6.63 min, $P < 0.001$). The cumulative pethidine requirement in 24-h duration was significantly less in group KL compared to group K and group L (58.85 ± 10.87 vs 91.3 ± 12.59 vs 68.9 ± 14.72 mg, $P < 0.001$). [Table 3]

Table 1: Demographic and clinical characteristics of study patients

Parameters	Group K	Group L	Group KL	*P* value
Mean age, y	43.95 ± 4.11	45.65 ± 3.69	43.55 ± 4.71	*P* = 0.25
Mean weight, kg	56.35 ± 10.00	57.78 ± 9.77	54.38 ± 8.73	*P* = 0.52
ASA grade				*P* = 1
I	80.00%	80.00%	80.00%	
II	20.00%	20.00%	20.00%	
Duration of surgery, min	105.1 ± 7.12	110.2 ± 5.10	111.4 ± 1.95	*P* = 0.06
Intra-operative requirement of fentanyl (μg)	169.05 ± 30.00	173.40 ± 29.37	163.25 ± 26.32	*P* = 0.53

ANOVA test

Table 2: Comparison of the postoperative Visual Analog Scale (VAS) score

Time point	Group K (*n* = 20)	Group L (*n* = 20)	Group KL (*n* = 20)s	*P* value
TP0	2.3 ± 0.46	2.25 ± 0.43	2.1 ± 0.3	0.289
TP15	2.35 ± 0.48	2.15 ± 0.36	2.1 ± 0.3	0.115
TP30	2.65 ± 0.91	2.25 ± 0.43	2.2 ± 0.4	0.060
TP1	2.7 ± 0.84	2.25 ± 0.43	2.2 ± 0.4	0.022*
TP2	3.55 ± 0.97	2.5 ± 0.59	2.35 ± 0.57	<0.001*
TP6	3.85 ± 0.85	3.4 ± 0.49	3 ± 0.63	0.001*
TP12	3.7 ± 0.56	3.4 ± 0.86	3.35 ± 0.65	0.259
TP24	3.8 ± 0.68	3.45 ± 1.24	3.5 ± 1.28	0.575

ANOVA test

*Significant

TP0, TP15, and TP30 are 0-, 15-, and 30-min postoperative time, respectively; TP1, TP2, TP6, TP12, and TP 24 are 1, 2, 6, 12, and 24 h postoperative time, respectively

Table 3: Comparison of pethidine requirement (additional analgesia)

Parameters (mean ± SD)	Group K	Group L	Group KL	*P* value
Time to the first dose of pethidine requirement (min)	32.5 ± 4.61	119 ± 6.63	363.25 ± 8.1	<0.001*
Mean cumulative pethidine (mg) [0–24 h]	91.3 ± 12.59	68.9 ± 14.72	58.85 ± 10.87	<0.001*

ANOVA test

*Significant

The hemodynamic parameters were thoroughly maintained in the three groups without in the range of 70–100 beats per minute and 90–110 mm of Hg [Figures 2 and 3].

The sedation score was limited to 1 in the three groups up to 30-min postoperatively, following which it kept on decreasing till it reached 0 at 12–24 h. The three groups showed significant differences only at the 1-h postoperative period ($P = 0.001$). [Table 4]

As for side-effects, 30% of patients in group K (i.e., six patients) had nausea. Out of these six patients who had nausea in group K, two patients had moderate nausea and four had mild nausea. In group L, 10% of patients (i.e., two patients) had mild nausea. There were no cases of nausea reported among patients in the KL group. No patient in any group had vomiting or hallucination as a side effect [Figure 4].

The patient satisfaction score was significantly greater in group KL (3.30 ± 0.57) as compared to both groups K (1.90 ± 0.44) and L (2.50 ± 0.60), $P = 0.0001$ [Figure 5].

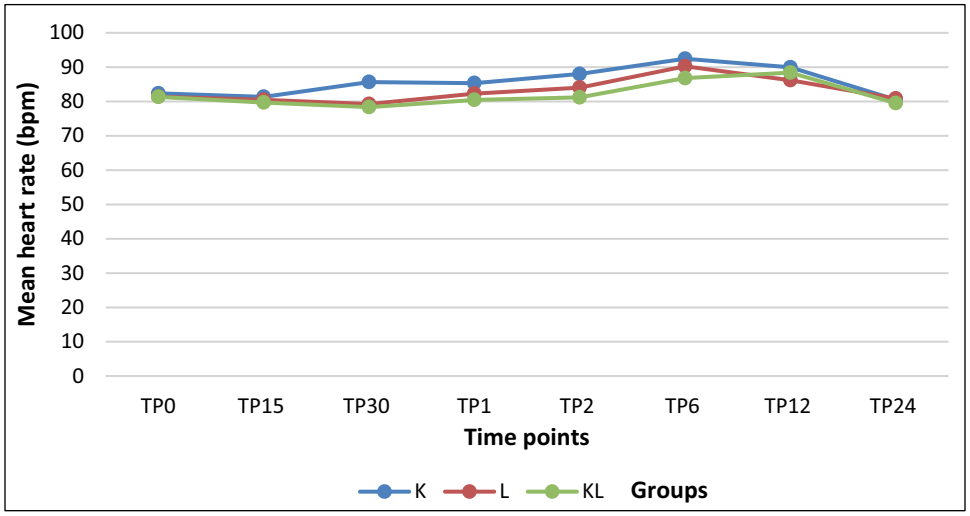

Figure 2: Comparison of the postoperative heart rate (HR) at various time points among the groups. TP0, TP15, and TP30 are 0-, 15-, and 30-min postoperative time, respectively; TP1, TP2, TP6, TP12, and TP 24 are 1-, 2-, 6-, 12-, and 24-h postoperative time, respectively

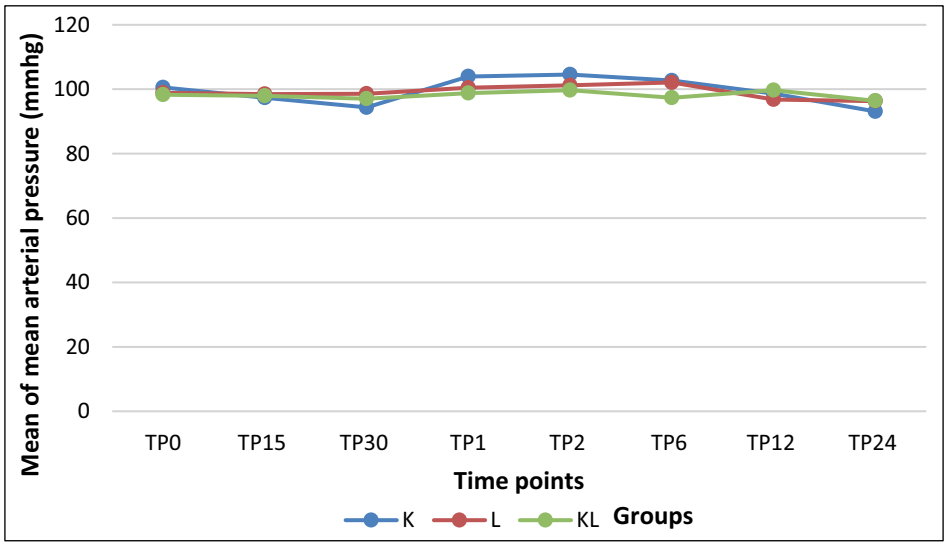

Figure 3: Comparison of postoperative mean arterial pressure (MAP) at various time points among the groups. TP0, TP15, and TP30 are 0-, 15-, and 30-min postoperative time, respectively; TP1, TP2, TP6, TP12, and TP 24 are 1, 2, 6, 12 and 24 h postoperative time, respectively

Table 4: Comparison of the sedation score among the groups at various time points

Time periods	K (*n* = 20)	L (*n* = 20)	KL (*n* = 20)	*P* value
TP0	1.20 ± 0.41	1.00 ± 0.00	1.05 ± 0.22	–
TP15	1.10 ± 0.30	1.00 ± 0.00	1.00 ± 0.00	–
TP30	0.90 ± 0.30	1.00 ± 0.00	1.00 ± 0.00	–
TP1	0.90 ± 0.30	0.05 ± 0.22	0.45 ± 0.51	0.001*
TP2	0.05 ± 0.22	0.00 ± 0.00	0.05 ± 0.22	–
TP6	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.22	–
TP12	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	–
TP24	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	–

ANOVA test.
*Significant.
TP0, TP15, and TP30 are 0-, 15-, and 30-min postoperative time, respectively; TP1, TP2, TP6, TP12, and TP 24 are 1, 2, 6, 12, and 24 h postoperative time, respectively

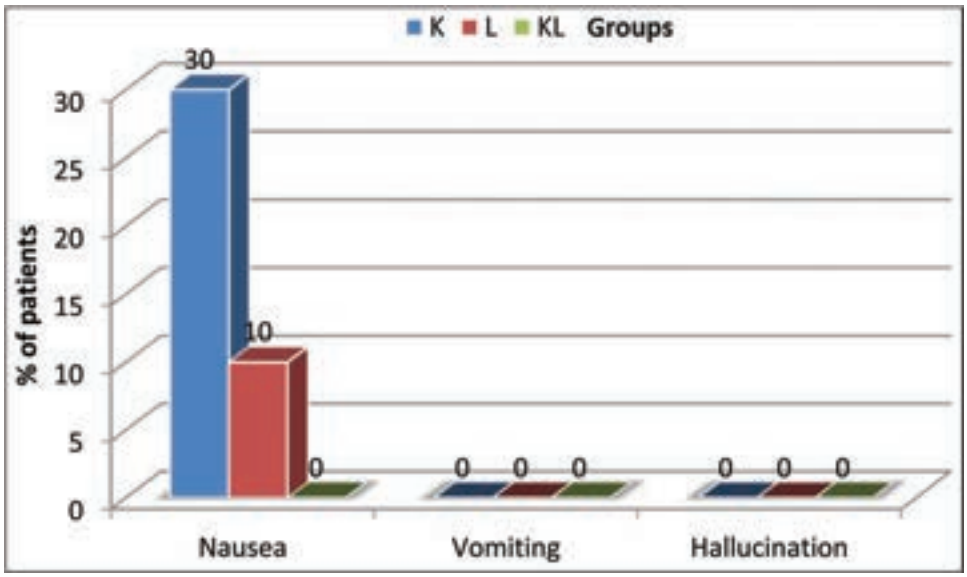

Figure 4: Comparison of side-effects

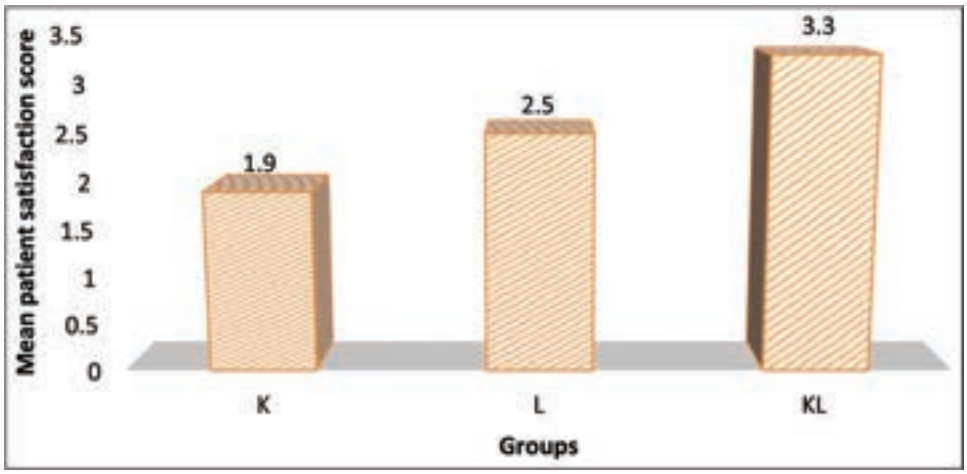

Figure 5: Comparison of patient satisfaction score among the groups. ANOVA TEST, *P* = 0.001*; *post hoc* tests: K vs L: *P* = 0.003*; K vs KL: *P* = 0.0001*; L vs KL: *P* = 0.0001*; **p* < 0.05, statistically significant

DISCUSSION

The present study results indicate that the incisional surgical infiltration by a combination of ketamine and levobupivacaine provides better postoperative pain relief until 24 h of abdominal hysterectomy, with better patient satisfaction and lesser requirement of total pethidine. Overall, the combination and individual use of ketamine and levobupivacaine were safe with limited side-effects of nausea and minimal sedation.

The current study results showed that the hypothesis of better efficacy and safety of the combinations of the drugs over the individual drugs holds true, as, with the combination of ketamine and levobupivacaine, the actions of both the drugs were combined, which provided a better long-lasting analgesic effect in the postoperative period with lower VAS pain scores among all the patients. This allowed for lesser use of early pethidine and total requirement of pethidine.

In terms of the efficacy, individual drugs that hold efficacy for pre-incision infiltration include bupivacaine,[13] levobupivacaine, ropivacaine, lidocaine, epinephrine, dexamethasone, opioids (like morphine, fentanyl, and meperidine), and NSAIDs like ketorolac and diclofenac.[7,14,15]

Moreover, studies have also compared groups K or L with other drugs. Rahman P *et al*[16] compared preoperative subcutaneous infiltration of ketamine and bupivacaine. Ketamine was found to be better than bupivacaine in terms of the mean pain score (5.2 ± 0.47 vs. 7.4 ± 0.68), mean sedation scores at 2 h (4.38 ± 0.57 vs. 3.52 ± 0.27, $P = 0.001$) and 6 h postoperatively (4.13 ± 0.32 vs. 3.89 ± 0.51, $P = 0.001$), and more stabilized heart rate.

In a study that compared ropivacaine, ketamine, and fentanyl as pre-incisional analgesics, the infiltration of ketamine led to improved hemodynamic parameters, better sedation, and significantly longest analgesic effect postoperatively.[17]

Bhola et al[18] compared the efficacy of ketamine and bupivacaine and found that ketamine was better in terms of inducing analgesic effects, with significantly lower pain scores at 8 (2.53 ± 0.50 vs. 3.7 ± 0.83), 10 (3 ± 0.52 vs. 4.67 ± 0.84), and 24 h (5.63 ± 0.67 vs. 7.47 ± 0.68) postoperatively ($P < 0.05$). Moreover, the ketamine group had a significantly higher time of requirement of first analgesia (155.8 ± 5.13 vs. 130.8 ± 8.08 min) and significantly lesser mean total dose of tramadol (185 ± 39.71 vs. 236 ± 40.01 mg) ($P < 0.05$).

In a study, levobupivacaine+ fentanyl (L + F) was compared with bupivacaine+fentanyl (B + F), where B + F was better at maintaining the heart rate postoperatively at 25 min (80.0 ± 14.0 vs. 73.0 ± 9.0, $P = 0.013$) and 35 min (77.0 ± 13.0 vs. 71.0 ± 8.0, $P = 0.032$) and better analgesia as there was a significantly higher time of analgesic requirement postoperatively (233.0 ± 20.0 vs. 161.4 ± 24.5 min, $P < 0.05$) and lesser cases of acute hypotension (27.5% vs. 50%, $P = 0.039$).[19]

Kaler *et al*.[20] compared the efficacy of the combination of ketamine+levobupivacaine with levobupivacaine and found that the combination had significantly higher time to first rescue analgesia (4.80 ± 2.24 vs. 3.29 ± 2.07 h, $P = 0.039$), lesser mean total opioid consumption (63.33 ± 22.89 vs. 96.55 ± 37.63 mg, $P = 0.003$), and significantly superior patient satisfaction score. Thus, they found the combination to be better than levobupivacaine alone in postoperative analgesia after LSCS.

This was also supported by Sharma P,[21] as the combination of ketamine+levobupivacaine proved to be better than levobupivacaine alone in terms of better analgesia with prolonged mean time to first rescue analgesia (4.97 ± 2.36 vs. 3.35 ± 2.21 h), lesser requirement of rescue opioid analgesia (45% vs. 95%), mean total opioid dose within 24 h (62.12 ± 23.67 vs. 97.63 ± 38.26 mg), more patients with excellent patient satisfaction score (24% vs. 7%), and no major side-effects. Therefore, these studies also found that the combination was superior to the use of individual drugs.

Besides efficacy, safety remains a major concern. In terms of side-effects, our study results showed that there were no cases of nausea and vomiting in the group KL as compared to two cases of nausea in Group L and six cases of nausea in Group K. This was in line with the observation in the study by Abdallah *et al*,[1] who observed minimal side-effects with ketamine (two patients had nausea, one had vomiting, and one had dizziness) and levobupivacaine group (one case of nausea and one case of dizziness). In another similar study, Talukdar et al[22] reported that there was a low incidence of adverse effects in both ketamine and levobupivacaine groups, with no significant difference among groups. In a different study involving patients who had lower number of Cesarean sections and received ketamine and levobupivacaine for postoperative pain management, the occurrence of nausea and vomiting was similar across the groups, with no significant differences observed ($P = 0.554$).[20]

Overall, we found that the concept of pre-incisional surgical site wound infiltration provides good analgesia

by prevention of central sensitization, which is triggered during surgical incision in abdominal hysterectomies. Similar to the present study, various previous studies have also found pre-emptive surgical site infiltration of the local anesthetic to be useful in decreasing the postoperative pain in surgeries like orthopedic surgeries, laparoscopic gynecological surgery, and hernia repair.[23,24]

To our knowledge, no previous study has been conducted where the combination of drugs was used and compared against ketamine and levobupivacaine alone in any type of surgery. As of now, research showed that two studies have been conducted comparing levobupivacaine against ketamine for pre-emptive surgical site infiltration in patients undergoing abdominal hysterectomy. Among them, Abdallah NM *et al*[1] found that ketamine was a better alternative to levobupivacaine since it provides significantly better delayed request of opioid analgesia and lesser opioid consumption with a lesser dose of meperidine used. Similarly, Talukdar *et al*[22] found that ketamine provided better postoperative analgesia, delayed first request for rescue analgesia, and lesser use of rescue analgesia in comparison with levobupivacaine in patients who underwent lower abdominal surgeries. This may be because ketamine is very specific in its mechanism of action and as it is an NMDA receptor antagonist and specifically reverses the central sensitization and decreases the postoperative pain. Also, it depresses the sodium channel function, leading to a local anesthetic effect. An additional inhibition of local inflammation has also been encountered with the use of ketamine where it prevents cytokine production, inflammatory mediator regulation, and infiltration of inflammatory cells.[1] In contrast to their results, at the individual level, levobupivacaine was found to be a better analgesic than ketamine in our study in terms of the need of total pethidine and postoperative pain levels (VAS score) in the postoperative stage. Similarly, the superiority of local infiltration of anesthetics for postoperative pain management was also proven in other recent studies,[25,26] making it an upcoming novel management technique for post-surgery pain.

Strengths of the study

The present study holds strength as it was a randomized study in three groups. The randomization in the present study ensured that all the baseline, demographic, and clinical characteristics were comparable in the three groups. Any differences in outcomes could be purely ascribed to the differential use of the drugs.

Limitations of the study

The study results must be interpreted under limitations of a small sample size and a specific type of surgery used. Moreover, comorbidities were not taken into account. The hospital stay of the patients was not assessed. The study did not assess the cost–benefit analysis of the drugs.

CONCLUSION

In conclusion, the combination of ketamine and levobupivacaine is a safe and efficacious alternative as pre-emptive analgesia among patients undergoing abdominal hysterectomies, against use of the individual drugs. The combination enhances the relief from postoperative pain and provides much better patient satisfaction, leading to better outcomes.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Local antituberculosis treatment in nonhealing chronic surgical site tuberculosis: A novel approach to cure nonhealing wound!

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Abstract

Tuberculosis most commonly affects the lungs and less than 20% of cases showed extrapulmonary involvement. Tuberculosis at the surgical site is described in the medical literature with very few cases of cesarean section at the incision site. Nonhealing surgical site ulcers secondary to tuberculosis are not widely reported in the literature and treatment options to heal these lesions are not described. Surgical site infections resulting to a slow or nonhealing wound are commonly reported and usually depend on various factors. Patient factors include the patient's immune status and comorbidities. Hospital management factors such as infection control policies in operation theatre, sterilization techniques for surgical instruments, and local wound care methods established and implemented by hospital staff. In this case report, a 34-year-old female with history of cesarean delivery 1 month back presented with nonhealing wound at the surgical site. We have done surgical repair with biopsy of wound margins. Wound discharge microscopy was negative for acid fast bacilli with few gram-positive cocci. Cartridge based nucleic acid amplification testes were positive for *Mycobacterium tuberculosis* genome. Histopathology shown tuberculous pathology and underlying chronic infectious process for nonhealing wound. We have offered antituberculosis treatment (ATT) as per protocol and observed healing of tuberculous ulcer after three months with reappearance of ulcer in fourth month of ATT. We have topically applied isoniazid and streptomycin over tuberculous ulcer along with systemic ATT. Tuberculous ulcer has responded and noted "cure" as completely healed surgical wound after 6 months of ATT with topical application of isoniazid and streptomycin.

Keywords: Acid fast bacilli, antituberculosis treatment, histopathology, surgical wound, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is one of the most ancient diseases of mankind and has co-evolved with humans for many thousands of years or perhaps for several million years.[1]

World Health Organization fact sheet on tuberculosis stated that overall, one-third of the world's population (over two billion) is currently infected with the TB bacillus.[2] TB is having significant impact on mortality and morbidity in

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in low- and middle-income countries (LMIC) where it generates a significant burden of disease.[3] India, China, Indonesia, South Africa, and Nigeria rank first to fifth, respectively, in terms of the incident TB cases. India accounts for highest number of new cases, and total cases on treatment across the world.[4]

CASE SUMMARY

A 34-year-old female, software engineer, no history of addiction, normotensive, nondiabetic, referred by a general surgeon and obstetrician for nonhealing surgical site ulcer at cesarean section site with histopathology showing tuberculosis etiology. Retrospectively, we collected data and found that she underwent a cesarean section just after orthopedic surgery on Pott's spine, previously in the same operation theater. On examination, the wound is typically chronic, nonhealing ulcer. Ulcer is variable in depth and is nonuniform in length, depth, and width across all cesarean section incisions. Base of the wound has a yellowish slough with unhealthy granulation tissue [Figure 1]. Histopathology analysis showed tuberculosis pathology. Typical tuberculous granuloma is undermined with fat cells and necrosed submucosa [Figure 2]. She was referred to our center for tuberculosis evaluation and treatment.

Routine hematological workup, chest X-ray, blood sugar, viral markers, and biochemistry analysis were within normal reference range. Ultrasound examination of abdomen does not show any abnormality in peritoneum or mesenteric nodes and urinary tract. Smear analysis of ulcer wash specimen was negative for acid fast bacilli (AFB). Cartridge base nucleic acid amplification test on ulcer wash specimen was positive for *Mycobacterium tuberculosis* (MTB) genome and rifampicin sensitive (rpo-b negative).

We have started antituberculosis treatment (ATT) as per the National Tuberculosis Elimination Program (NTEP) protocol according to the weight band containing four drugs isoniazid (H), rifampicin (R), ethambutol (E),

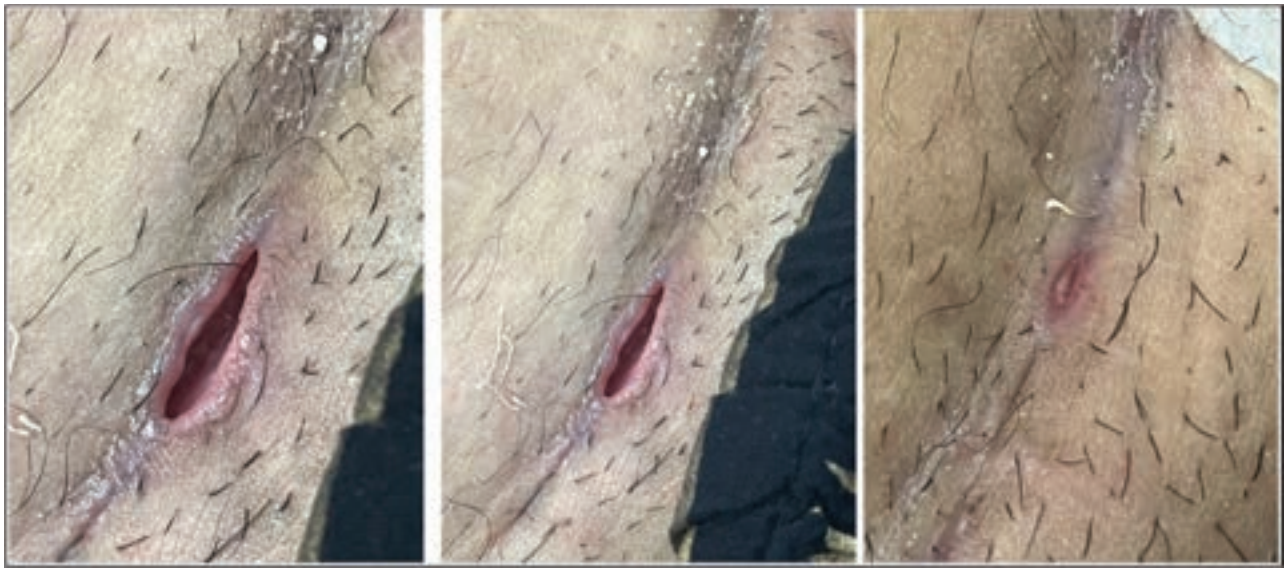

Figure 1: Healthy surgical wound with slough and ulceration at cesarean section incision

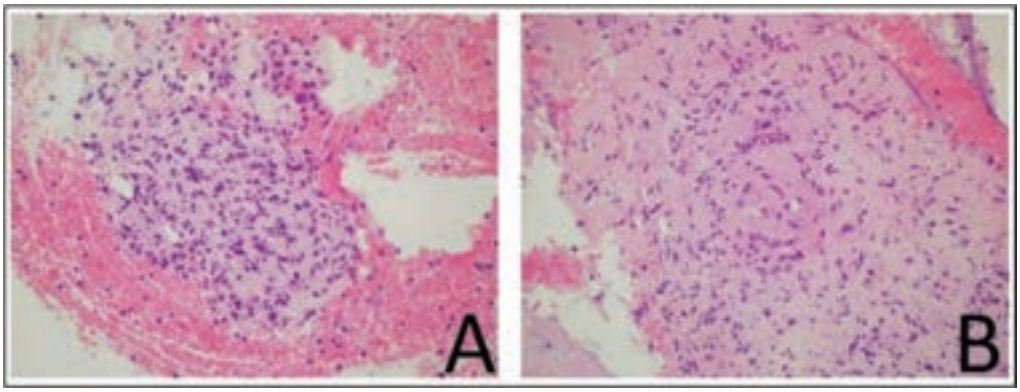

Figure 2: Histopathology of surgical site nonhealing ulcer

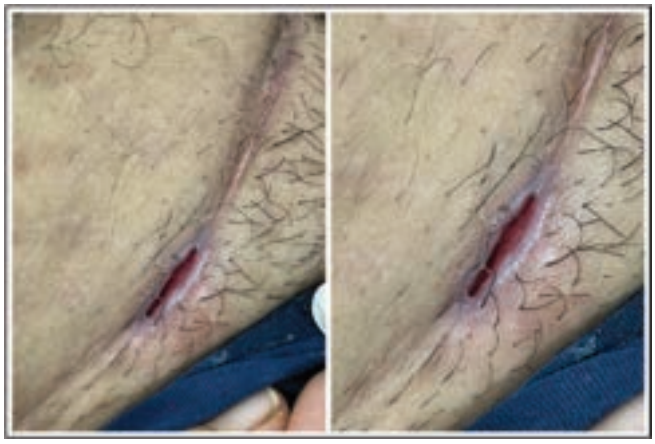

Figure 3: Burst of healed tuberculous ulcer resulting into reappearance of untidy wound with discharge after four months of treatment

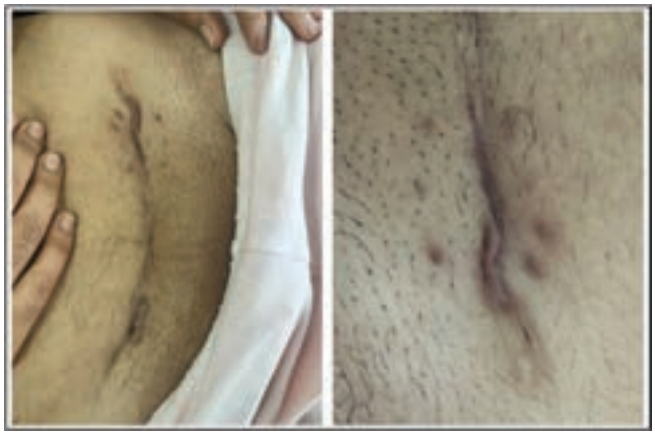

Figure 4: Healed tuberculous ulcer with hypertrophied scar after 6 months of treatment

and pyrazinamide (Z). We have documented significant improvement in tuberculous ulcer and noted a decrease in size, induration , anddischarge. She has noted reappearance of the wound in third month with discharge and local pain, as noted before ATT initiation [Figure 3].

This time we have decided to add topical antimycobacterial drugs in tuberculous ulcer treatment along with systemic oral drugs isoniazid, rifampicin, ethambutol. We have suggested to crush two isoniazid 300 mg tablets to make a powder and apply it four to five times in divided doses after mixing it with the powder of an injection of 750 mg streptomycin injection. We have applied mixture of two isoniazid tablets with one streptomycin injections daily as a treatment protocol along with systemic oral full dose ATT. We have documented complete healing of surgical wound in one and half months [Figure 4].

DISCUSSION

Surgical site infection is defined as an infection of the superficial or deep skin incision, or of an organ or space, occurring up to 30 days after surgery if no implant was left behind, or within one year if an implant was left in place.[5] Surgical site infection (SSI) is one of the risks that women may experience after a caeserian section procedure. It is an infection that occurs at the incision/operative site within 30 days of the post-surgical procedure.[6] Globally, SSI is the second most reported health-care associated infections (HAI) accounting for 19.6% of the HAIs.[7] Tuberculosis at surgical site tuberculosis is previously documented in various case reports and case series.[8,9] Local curative role of ATT is less frequently reported in the published medical literature and observed in few case reports with topical application of isoniazid ointment.[10]

OUR PROTOCOL IN THIS CASE REPORT

1. Isoniazid 300 mg two tablets crushed to make powder.
2. One injections of Streptomycin 750 mg vial taken and powder separated from vial.
3. Mixture of two tablets of isoniazid and streptomycin powder made as one preparation.
4. This preparation of two medications applied five to six times in a day or within 24 h.
5. Next day again we have prepared the same procedure and prepared dry powder mixture.
6. No other antiseptics were used while applying these dry powder mixture.
7. Dry gauze or saline wash can be given if required to clear scabs over surgical wound.
8. Utmost precautions taken to prevent moisture in dry powder mixture and every time powder applied to the deepest portion of wound to increase penetration of drugs to local site.
9. Systemic course of ATT as per schedule is continued along with topical ATT for successful treatment outcome.

CONCLUSION

In present case report, we have documented post cesarean section nonhealing wound caused by *Mycobacterium tuberculosis*. We have offered topical application of isoniazid and streptomycin along with systemic ATT and documented complete healing of ulcer and documented cure after six months of treatment.

Key learning points from this case report are the following:

1. Nonhealing wounds at post-surgical site requires proper workup such as routine microscopy and culture sensitivity of wound discharge, wound discharge smear for acid fast bacilli and nucleic acid amplification test analysis in discharge.

2. Histopathological evaluation of wound margins is the gold standard test to confirm etiological factors associated with nonhealing wounds. Histopathology sample for smear, cartridge based rapid diagnostic nucleic acid amplification tests may not give positive yield to diagnose tuberculosis.
3. Response to antituberculosis treatment may be there but usually unpredicted due to less penetration of drugs in local nonhealing wound due to necrosis and slough in the tuberculous ulcer.
4. Topical antituberculosis medicines are not routinely used even in tuberculosis of skin. In tuberculous ulcer and implant tuberculosis, topical or local application of antituberculosis drugs such as isoniazid and streptomycin has documented complimentary effect in healing when given along with systemic ATT.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Plexiform schwannoma of penis

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Abstract

Schwannoma is a very rare tumor and mostly benign in nature. it may be associated with neurofibromatosis 2 (NF2). This variant involves the head and neck most commonly, and rarely involves the penis. The patient was 32 years old and presented to us with a 2 cm × 2 cm lesion at the right lateral aspect of the penis just proximal to the glans from the past 2 years. He was evaluated with ultrasound and MRI and mistaken for hemangioma. In view of hemangioma, one session of intalesional 3% sodium tetradecylsulphate was infiltrated. There was no decrease in size on follow-up. Excision of the lesion was planned, and histopathology and immunohistochemistry were suggestive of plexiform schwannoma. The postoperative period was uneventful with normal voiding and erection on follow-up. Plexiform schwannoma is rare in the genital region. This is highly vascular so can be mistaken for hemangioma. Excision is the method of treatment and along with histopathological evaluation is the main stay of diagnosis. The patient should be followed for recurrence.

Keywords: Penile region, plexiform variant, schwannoma

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INTRODUCTION

Schwannoma is a rare tumor arising from schwann cells that support the peripheral nervous system. Schwannoma is the most common type of peripheral nerve sheath tumor having predilection for the head and neck. The genital region is a rare site for schwannoma. Isolated schwannoma of the penis is rare and may be mistaken for hemangioma. Schwannoma is a benign disease but may become malignant rarely. Schwannoma may be associated with genetic disorders—neurofibromatosis type 2 (NF 2) and carney complex.[1] There is no age, gender, or racial predilection. Diagnosis is made by imaging and biopsy. German histologist and physiologist, Theodor Schwann described schwannomas which originate from myelinating cells of the peripheral nervous system and are composed of schwann cells.[2] Parra reported the first case of solitary neurinoma of the glans penis in 1968 in a dermatology article in German.[3]

CASE PRESENTATION

A 32-year-old male presented with painless small swelling at the right lateral aspect of the penis which was just proximal to glans. Swelling gradually increased in size and reached to size of 2 cm × 2 cm over 2 years. The patient had normal erection and no lower urinary tract symptoms. There was no significant history of trauma to the penis or scrotum and without family history of swelling over the body or neurofibromatosis type 2. He had a history of intake of antitubercular medication in 2014 (defaulter) and 2022 (completed course) for pulmonary tuberculosis. He has been on antipsychotic medication since January 2022. On examination, a 2 × 2 cm nontender, smooth,

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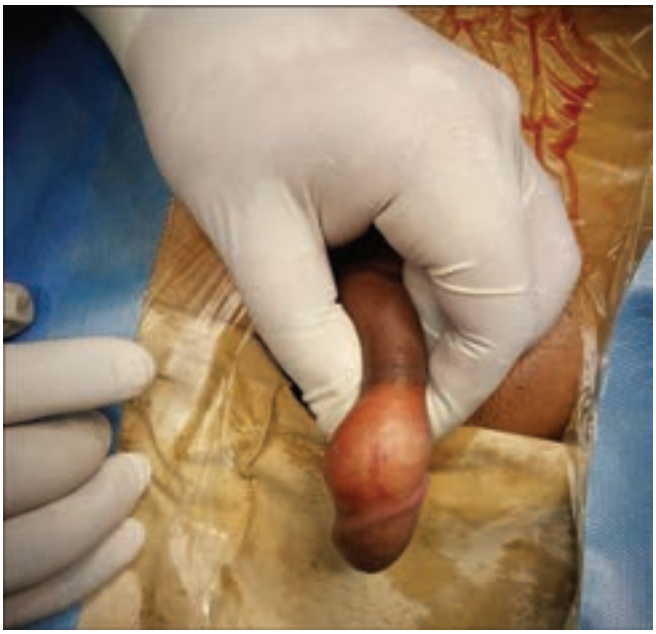

Figure 1: Space occupying lesion (SOL) at the right lateral aspect of penis

regular, firm, mobile mass present 1 cm proximal to coronal sulcus at the right lateral aspect of penile shaft which was not fixed to overlying penile skin but with restricted mobility with erectile tissue. There was a single superficial vessel running over the mass [Figure 1]. The penile shaft was deviated to the left side with curvature being on the right side. Bilateral inguinal lymph nodes were not palpable. No similar lump was present at any other site of the body. Baseline blood and urine reports were essentially normal.

Doppler ultrasound revealed 2 cm × 1.03 cm × 2.10 cm lesion with heterogenous echogenicity in interfascial plane (between superficial and Buck's fascia). The lesion has internal hypoechoic areas with few cystic spaces and has color flow on doppler study which was suggestive of vascular malformation. MRI of the penis was done which revealed ill-defined (T1W: dark, T2W: bright) soft tissue lesion (size: 19 mm × 14 mm) at the right lateral margin of the distal penis arising just proximal to the glans with mild enhancement and no definite source tissue could be defined. The impression was of hemangioma.

Based on clinical examination and investigation, the patient was planned for intralesional 3% sodium tetradecylsulphate.[4] 1 mL of intralesional sodium tetradecylsulphate was infiltrated with 26 G needle along with tourniquet applied at the base of the penis. For the next session, patient did not give consent. He was examined after 3 weeks and there was no decrease in size and the patient was planned for excision of the lesion. After explaining the procedure and taking informed consent, the patient was posted for surgery.

Under spinal anesthesia, a supine position was made. Part prepped with povidone–iodine solution (10% w/v) and drapped. Circumcoronal incision made with degloving of skin. Wide local excision of the lesion has been done with 0.5 cm of negative margin. It involved the corpora, and urethra at right lateral margin (intra-op findings were 2 × 2 cm, well defined, over the right lateral aspect of distal penile shaft (~1 cm proximal to coronal sulcus), free from overlying skin but invading to tunica albuginea, corpora and urethra. Corpora and urethra were repaired with 3-0 polyglactin suture. Tunica albuginea was approximated with a 2-0 polyglactin suture. On excision, the lesion was 2 cm in size, firm, and with smooth surface and regular margin.

HISTOPATHOLOGICAL EXAMINATION

Hematoxylin and eosin (H&E) staining revealed alternate acellular and hypercellular area ([Figure 2A]—100×, [Figure 2B]–400×).

On immunohistochemistry, CD 34 ([Figure 3A]—100×) and s-100 ([Figure 3B—100×, Figure 3C]: 400×) was strongly positive.

During the follow-up of 8 weeks, the patient had no complaints of voiding and erection was normal.

DISCUSSION

Schwannoma can occur in any part of the body. To the best of our search, 40 cases of penile schwannoma have been reported do date and very few cases were plexiform penile schwannoma.[6,12] Among different histological subtypes of schwannoma, plexiform schwannoma is one of them. This variant involves the head and neck region most commonly[5] and the genital region being rarely involved.[6,7] Benign entity is more common and can be familial as in neurofibromatosis 2 (NF2). Plexiform schwannoma may not be associated with von Recklinghausen's disease and is rarely malignant.[8] Penile schwannoma is rare and can be mistaken for hemangioma as it has good vascularity.[9] CECT and MRI show lesions with good vascularity and its relation to nearby structures. The possibility of peyronies disease, lipoma, lymphoma should be considered. The lesion should be treated with surgical excision and also for histopathological confirmation of diagnosis.[10] The patient should be followed for recurrence and surgical complications and managed accordingly. However, after negative surgical margin, recurrence rate is very low but can recur with positive margin.[11]

Our case has been evaluated with ultrasound and MRI of the penis and was managed with excision of the lesion.

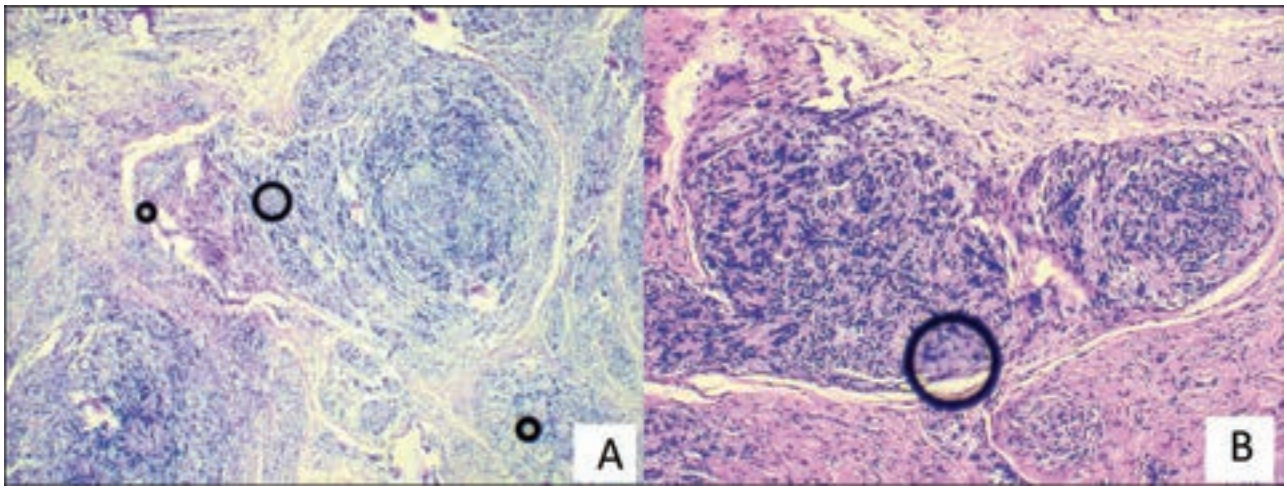

Figure 2: (a) 100×, showing acellular and hypercellular area, (b) 400×, showing acellular and hypercellular area

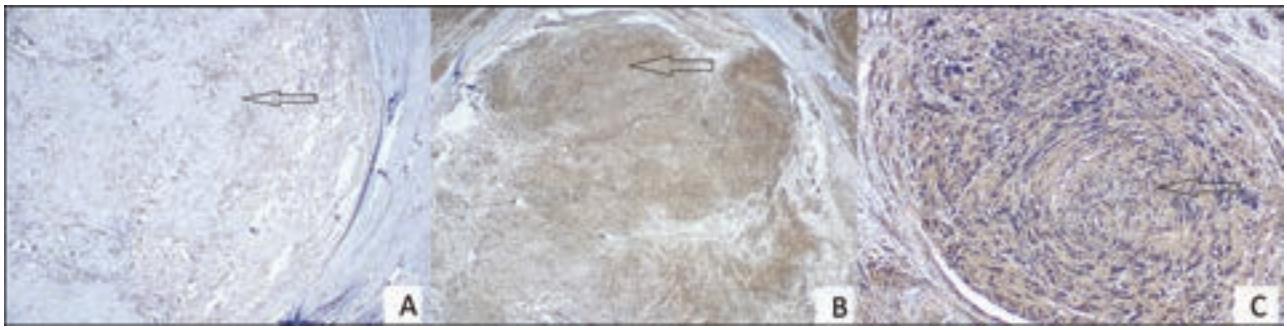

Figure 3: (a) IHC: CD 34, 100×, (b) s-100, 100×, (c) s-100, 400×

Histopathological examination was suggestive of plexiform schwannoma which is a rare subtype of schwannoma occurring in the penis. Other reported cases were also treated with excision of the lesion and for histopathological diagnosis.[9,12,13]

CONCLUSION

Penile schwannoma is a rare tumor, mostly benign. Surgical excision for treatment and diagnosis is most commonly performed at present. Further studies of penile schwannoma will guide the different approaches to treatment and follow-up of the patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Watch what you eat: Two cases of fish gall bladder induced acute kidney injury

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Abstract

The use of dehydrated and processed fish gallbladder as a traditional remedy has been associated with adverse effects on health. This report presents two cases of individuals who experienced anuric acute kidney injury and severe hepatitis after consuming fish gallbladder. Both patients received hemodialysis and steroid treatment, leading to full recovery of renal function and hepatic enzyme levels within 1 month.

Keywords: Fish, gall bladder, kidney injury

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INTRODUCTION

Dehydrated and well-processed fish gallbladder is touted as a traditional remedy for a variety of diseases.[1] It has been widely documented that fish gallbladder causes acute renal damage and ischemic hepatitis, both of which are completely reversible if caught early.[2] We report here a series of two cases of anuric acute kidney injury and severe hepatitis caused by the consumption of fish gallbladder, both of which recovered fully after a few sessions of hemodialysis.

CASE REPORT

The first case is of a 40-year-old mechanic with no known previous comorbidity. He had been complaining of lower back pain for a few days, and during a regular blood test, he was found to have elevated glucose, which was normal on a repeat blood test. For the above, he consumed cooked fish gallbladder twice a day for 3 days. After 4 days of consumption, he developed vomiting, pain in the abdomen, and reduced urine output, which was less than 100 mL for the next 3 days, while on the day of presentation, he was anuric. Routine investigations showed severe renal dysfunction (creatinine – 13 mg/dL), severe hyponatremia (117 mmol/L), hepatitis (SGOT – 900), and severe metabolic acidosis. Urine analysis revealed numerous WBCs and RBCs, and no eosinophils were detected.

He was given slow, low-efficiency dialysis for 1.5 h for two continuous days with serial monitoring of sodium. Further, one session of hemodialysis was done for 4 h, and a renal biopsy was done. He was pulsed with methylprednisolone 500 mg/day for 3 days and given oral prednisolone 0.5 mg/kg for 2 weeks. Renal biopsy showed acute tubular necrosis and acute interstitial nephritis with no interstitial fibrosis and tubular atrophy [Figure 1].

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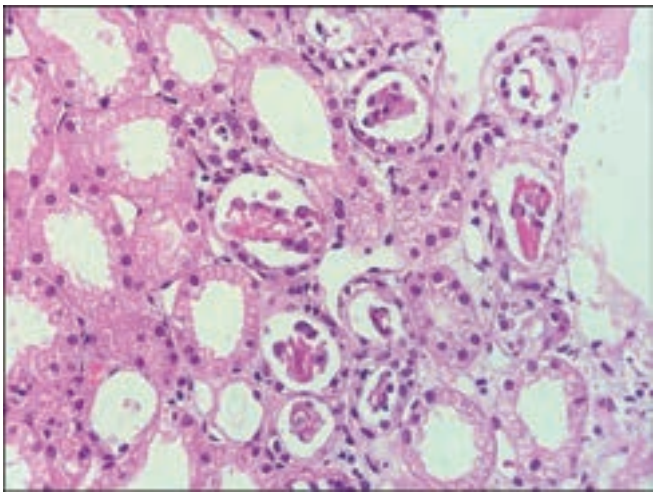

Figure 1: Renal biopsy on light microscopy, hematoxylin-eosin stain (400×) showing acute tubular necrosis and acute interstitial nephritis

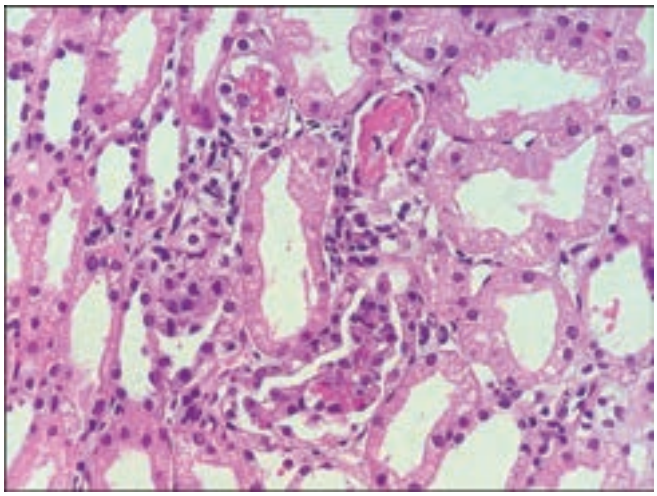

Figure 2: Renal biopsy on light microscopy, hematoxylin-Eosin stain (400×) showing severe acute tubular necrosis and lymphocytic infiltration of the interstitium suggestive of acute interstitial nephritis

His urine output gradually started to improve after 7 days. Serial monitoring of hepatic enzymes and serum creatinine was done, which showed gradual reduction and normalization at the end of 3 weeks. He continued on regular follow-up, and at the end of the first month, his serum creatinine was 1.22 mg/dL, and normal hepatic enzymes, while he continued to have adequate urine output.

The second case is of a 32-year-old fisherman who had no previously known comorbidities had raw fish gallbladder for general health benefit for 4 days. He developed severe vomiting and pain in his abdomen around 5 days later. He noted a reduction in urine output in the last few days. Routine investigations showed severe renal dysfunction (creatinine – 7.8 mg/dL) and severe anicteric hepatitis. Investigations for tropical infections were all negative, and as urine output started reducing over the next few days with rising creatinine with a peak of 10.8, he underwent 3 days of hemodialysis, followed by renal biopsy. Renal biopsy showed severe acute tubular necrosis with interstitial nephritis with no interstitial fibrosis and tubular atrophy [Figure 2].

He required two more sessions of hemodialysis on the next two alternate days in view of his persistent oliguria. His urine output started to improve a few days after the last hemodialysis session. He was pulsed with methylprednisolone 500 mg/day for 3 days and given oral prednisolone 0.5 mg/kg for 4 weeks and tapered over another 2 weeks. Serial measurement of hepatic enzymes and serum creatinine showed gradual improvement and normalization by the end of the month.

Both patients had complete recovery of renal function and hepatic enzyme levels at the end of 1 month of the illness and continued to do well on follow-up visits.

DISCUSSION

Various components of the fish have been used in traditional medicine to improve vision, night blindness, bronchial asthma, rheumatism, chronic illness, dyspepsia, and overall health. In particular, fish gallbladder has been specifically used to treat chronic kidney disease.[3]

Although fish gall bladder can produce serious systemic issues, poisoning does not always occur. Gall bladder from smaller fish is ingested on a regular basis in rural south-eastern countries with no apparent harm, while it is proposed that the toxicity is proportionate to the size and quantity of gallbladder or bile eaten.[4]

Cypriniformes fishes such as common carp (Cyprinouscarpio), grass carp (Ctenopharyngodonidella), Indian carp (Labeorohita), and silver carp Hypophthalmichthysmolitrix) have been linked to hepatorenal syndrome.[5] The main bile salt in Cyprinids (carp fishes) is bile alcohol sulfate. The major toxin responsible for fish gallbladder-associated acute kidney injury is thought to be water-soluble sodium cyprinol sulfate. It can also damage the heart, liver, and gastrointestinal tract.[6]

Sodium cyprinol sulfate causes direct toxic damage to the lysosome and targets the kidney, liver, heart, and gastrointestinal system. Cyanide and histamine both inhibit cytochrome oxidase, preventing cellular energy consumption and resulting in necrosis of tubular epithelial cells in the proximal tubule. [7]

Renal biopsies in patients with severe renal impairment caused by fish gallbladder ingestion typically reveal patchy

tubule cell necrosis with varied amounts of interstitial inflammation, while the histopathological findings are focal hepatitis in patients with associated liver injury[8]

Most patients require renal replacement therapy with hemodialysis, but there have been case reports of patients recovering with only conservative management and not requiring hemodialysis.[9] It is critical to treat acute tubular necrosis correctly. The prognosis is favorable with most documented cases achieving normal renal and hepatic function and no severe long-term consequences.[10]

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Testicular dislocation: Does timing of detection dictate management? A report of two cases

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Abstract

Testicular dislocation is a rare condition after blunt trauma to the pelvis and genitalia. It is often overlooked during initial management after trauma, and patients have been reported to present with the condition after months or years after the trauma. Diagnosis is confirmed by imaging, and management is primarily surgical. However, if patients present early with absence of other injuries requiring surgery, a manual reduction can be attempted to reposition the testis. Early management prevents testicular atrophy and spermatogenic dysfunction. Hence, a physical examination of the groin and genitalia should be mandatory in all patients with high energy trauma to the pelvis and genitalia.

Keywords: Manual reduction of testis, testicular dislocation, testicular trauma

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INTRODUCTION

Testicular dislocation is an uncommon sequelae of blunt trauma to the groin, resulting in extrusion of the testis outside its normal location in the scrotum. It is a rare entity, with less than 200 cases reported worldwide since it was first described over 200 years ago. We present two such cases of testicular dislocation detected at different periods of time following the initial trauma. We explored the options of management and discovered that the timing of detection and presentation is crucial, as the management changes totally depending on the time of presentation following trauma.

Case 1

A 29-year-old male patient had a motorbike accident 3 months ago leading to a fracture shaft femur. He underwent surgery for the same. He presented to our outpatient clinic 3 months later with the complaint of "disappearance" of both testes from the scrotum since the accident. He also stated that both testes were present in the scrotum before trauma. There was no record of clinical examination findings of the inguinoscrotal region following trauma.

Clinical examination revealed an empty normotrophic scrotum indicating that testes were in normal position before trauma. Globular swellings were palpable near the right deep inguinal ring and left inguinal canal [Figure 1]. Ultrasound sonography (USG) revealed presence of both the testes in the inguinal canal with normal vascularity. Contrast-enhanced computed tomography (CECT) was

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done for documentation of the location of the testes, which corroborated with the USG findings [Figure 2].

Following failure of attempt at manual reduction under intravenous opoid analgesics, bilateral inguinal canal was explored under regional anaesthesia. Both testes, with normal size and vascularity, were found in the superficial inguinal pouch. They were dissected free from surrounding structures, placed in the subdartos pouch and fixed to prevent torsion [Figure 3]. Following an uneventful postop period, patient was discharged the next day. Patient has since been on follow-up for 2 years, with no complications and preserved spermatogenic function.

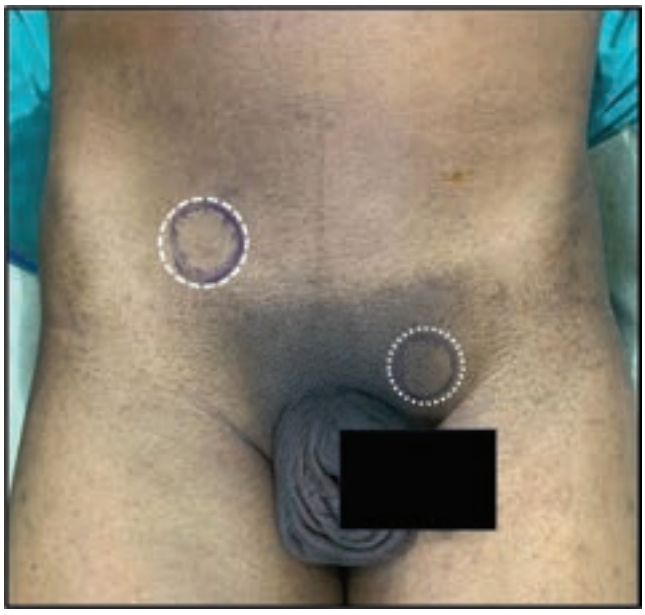

Figure 1: Case 1: Clinical image showing bilateral normotrophic, empty scrotum with palpable testes near the right deep inguinal ring and left inguinal canal

Case 2

A 24-year-old male presented with degloving injury of the penis following a motorbike accident. On examination, the right hemi-scrotum was found to be devoid of the testis, which was palpated in the right groin just above the superficial inguinal ring [Figure 4]. The left testis was in its normal position. USG color Doppler showed normal vascularity of the testis in the right superficial inguinal pouch with no other associated injuries.

Since, the patient presented within 6 hours of injury and USG ruled out any other injuries, manual reduction was successfully performed to manipulate the testis back into the right hemi-scrotum. Post repositioning, USG confirmed the position and vascularity of the testis. The patient had no subsequent complications, and spermatogenic function was preserved on one year follow up.

DISCUSSION

Testicular dislocation can be defined as an abnormal displacement of a normally located testis outside the scrotum usually after blunt trauma to the genitals. First described by Claubry[1] in 1809, it is a rare occurrence with only about 180 cases reported till date.[2] Most patients have a history of high energy collision while on a motorcycle

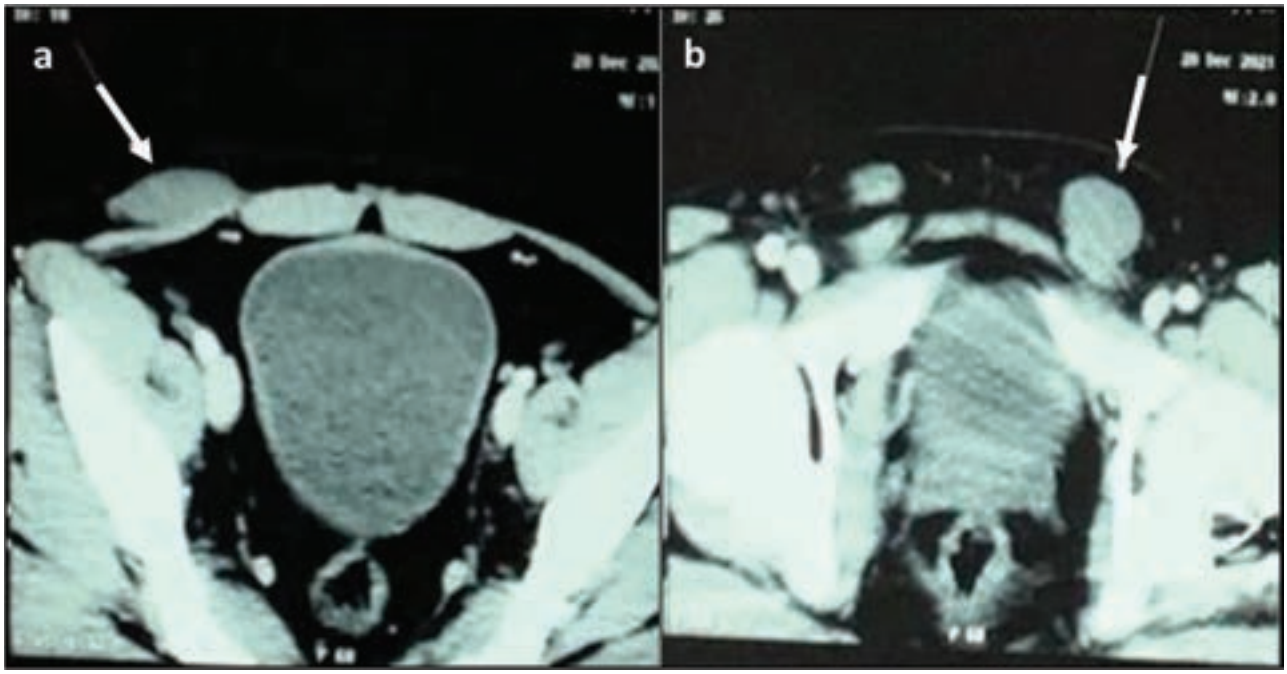

Figure 2: Contrast-enhanced computed tomography showing the location of bilateral testes (marked by arrows)

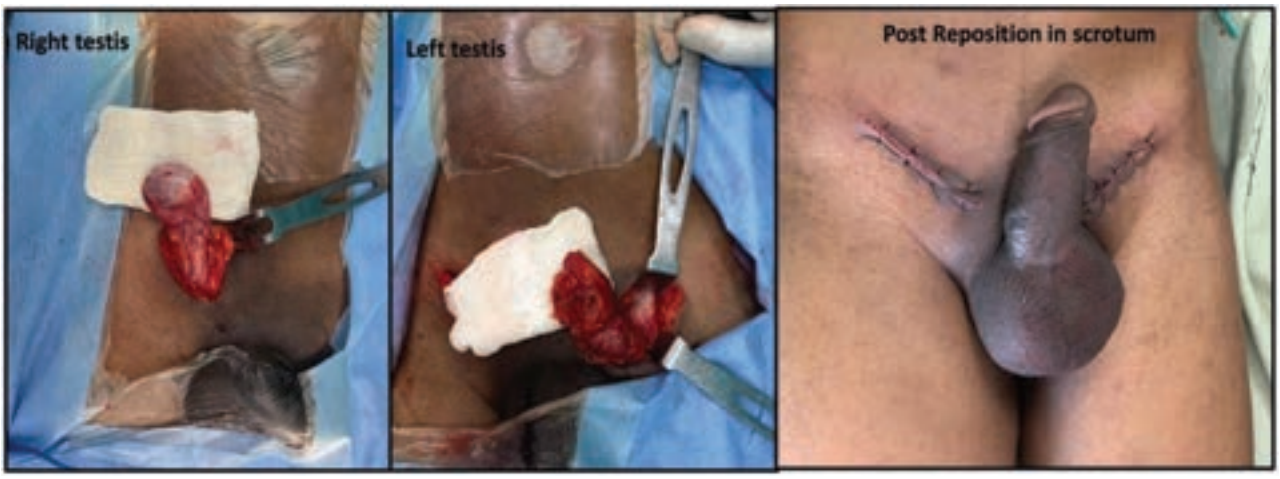

Figure 3: Intraoperative image after dissection of bilateral testes and repositioning in scrotum.

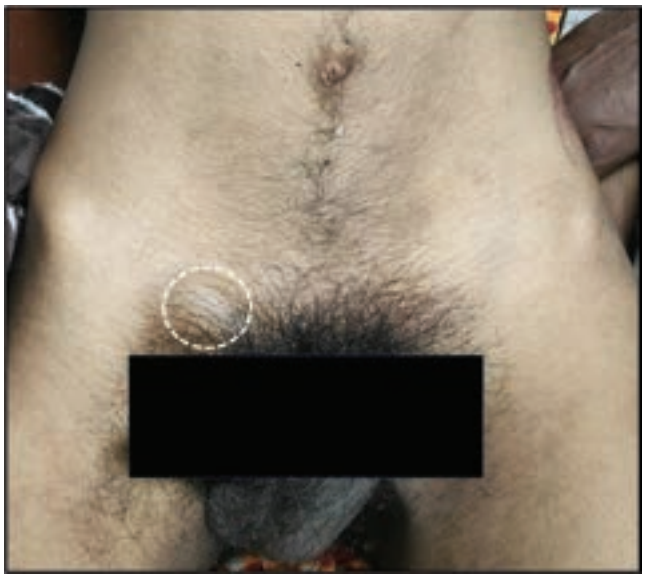

Figure 4: Case 2: Right normotrophic, empty hemi-scrotum with palpable testis just above the superficial inguinal ring

leading to sudden contraction of the cremaster, breach in the layers of the spermatic cord, and extrusion of the testis outside the scrotum.[3] The high impact of injury often leads to other associated injuries such as torsion, rupture, epididymal avulsion, pelvic fracture, and urethral injuries.

Testicular dislocation can be both unilateral and bilateral with up to one-third cases occurring bilaterally.[4] A detailed history from the patient regarding the presence of the testes in its normal location before trauma helps in differentiating it from undescended or a retractile testis. The dislocated testis is most commonly present in the superficial inguinal pouch,[5] although it can also be dislocated into the inguinal canal via the superficial ring, or in rare cases intra-abdominally. The exact site and mechanism of injury along with anatomical factors ultimately decide the laterality and site of dislocation.

The absence of the testis in the scrotum along with a palpable lump in the groin following trauma warrants an USG and Doppler study. USG can help in identifying the position of the testis following trauma, as well as associated injuries such as testicular rupture, torsion, epididymal avulsion, and helps to assess the viability of the testis.[6] In some cases when there is doubt in diagnosis, a computed tomography maybe performed.

A manual reduction should be the first line of management in early presentation of testicular dislocation.[7] In most patients, no anaesthesia is required while attempting manual reduction. However, if patients complain of pain or discomfort intravenous opioid analgesics may be given. Reported rates of successful repositioning are as low as 15%,[4] possibly due to a small defect size in spermatic fascia, retraction of tissue, and edema. A USG is a must before manual reduction to rule out associated injuries, in which case surgery is advisable. Success rates of closed reduction in patients with late symptom presentation are low due to the presence of edema and adhesions with the surrounding tissue. After reduction, a repeat USG should be performed to confirm the position of the testis and to rule out any injuries during reduction.

Surgical exploration is the mainstay of management in patients with failure of closed reduction, delayed presentation, and presence of other associated injuries. Early repositioning prevents testicular ischemia, atrophy of seminiferous tubules, impairment of spermatogenesis, chronic discomfort, and infertility.

For our first patient, a surgical exploration was necessary as he presented with the condition months after trauma. However, the second patient could be managed via a closed reduction after ruling out any other injuries on USG, as he presented within hours of the dislocation.

CONCLUSION

Testicular dislocation is an often-missed injury following a high-impact injury to the groin and genitalia. Early detection and management are important to prevent complications and preserve testicular function.

Time of detection is important in planning management as early detection with no other associated injuries can be given a trial of closed reduction with surgical exploration reserved for failure, delayed diagnosis, or in the presence of other injuries requiring surgery.

Examination of the groin should be mandatory during assessment of all patients with high energy trauma to the pelvis to avoid missing this uncommon clinical condition.

Declaration of patient consent

Consent has been taken from the patients for publishing their data and anonymized images.

Author contributions

The manuscript was conceptualized by SC. The first draft was prepared by SS, which was modified by SC. All three authors approved the final draft before submission.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Ectomesenchymal chondromyxoid tumor: A rare case report

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Abstract

Ectomesenchymal chondromyxoid tumor is a very rare tumor, which mostly occurs in the tongue. Here, we are presenting a case of a 55-year-old man with a swelling in the anterior dorsum of his tongue. The mass was excised and subsequent histopathological examination revealed a subepithelial well-circumscribed mass comprising oval to fusiform tumor cells, arranged in sheets, whorls, and reticular pattern within a prominent chondromyxoid stroma. The tumor cells were positive for glial fibrillary acidic protein, S100, and vimentin, whereas negative for epithelial membrane antigen and p63 on immunohistochemistry. These tumors have to be differentiated from other myxoid lesions, such as oral focal mucinosis, nerve sheath myxoma, soft tissue myxoma, glial choristoma, and ossifying fibromyxoid tumor of soft parts.

Keywords: Chondromyxoid stroma, ectomesenchymal chondromyxoid tumor, GFAP

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INTRODUCTION

Ectomesenchymal chondromyxoid tumor (ECT) is a very rare tumor mostly occurring in the tongue. At present, 60 cases have been reported in various research studies.[1,2] Here, we take the opportunity to report a rare case of ECT in the anterior dorsum of the tongue, in a 55-year-old male along with its histological differential diagnosis.

CASE REPORT

A 55-year-old male patient presented to the Ear, Nose, Throat (ENT) outpatient department of a tertiary care hospital, with a swelling in the dorsum of the anterior tongue for 2 years.

The swelling was asymptomatic but the patient was having difficulty during eating.

Clinical examination revealed a swelling of 0.5 cm in maximum dimension, soft and cystic in consistency with no skin changes.

After acquiring proper consent from the patient, a wide local excision was done in the ENT Department and, subsequently, sent for histopathological examination to the Department of Pathology.

On gross examination, a reddish globular mass measuring 1 cm × 0.5 cm was noted. The Cut section showed a solid cystic lesion with mucoid areas.

Microscopic examination [Figure 1] revealed a subepithelial well-circumscribed tumor lesion composed of lobules of tumor cells separated by fibrous bands and multiple slit-like clefts. Individual tumor cells are round to fusiform in

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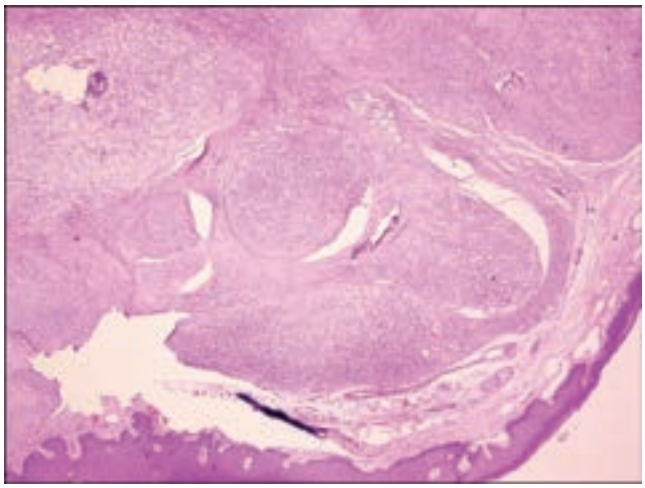

Figure 1: Sub epithelial lobules fusiform tumor cells (100×, hematoxylin and eosin)

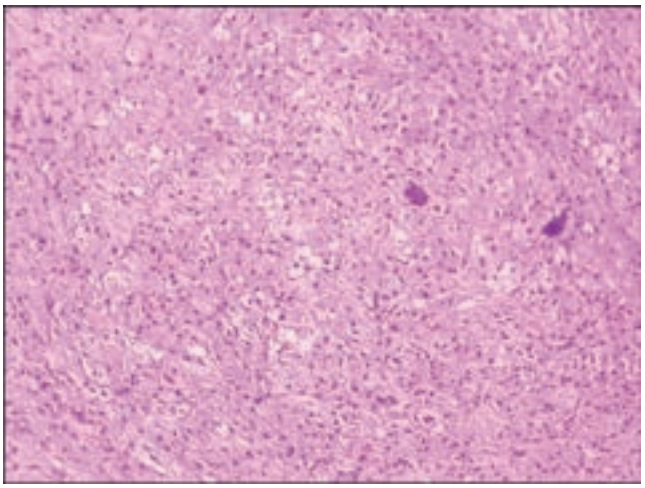

Figure 2: Prominent chondromyxoid stroma (400×, hematoxylin and eosin)

shape, have a moderate amount of eosinophilic cytoplasm, and have minimal pleomorphism. The cells were arranged in cords and sheets and dispersed within a prominent chondromyxoid stroma. No necrosis or mitosis was noted [Figures 2 and 3].

On performing immunohistochemistry (IHC) [Figure 4], the tumor cells were positive for glial fibrillary acidic protein (GFAP), S100, and vimentin, whereas negative for epithelial membrane antigen and p63.

DISCUSSION

ECT is a very rare tumor with an average age of 40 years and affects males and females equally. This tumor almost always affects the dorsum of the tongue. Very rare cases have been reported in the hard palate and posterior tongue.[1,2] The clinical differential diagnosis for ECT would include benign mesenchymal proliferations, such as fibrous hyperplasia, myofibroma, neurofibroma, granular cell tumor, schwannoma, leiomyoma, or rhabdomyoma.[3]

Histologically, it must be differentiated from myxoid lesions, such as oral focal mucinosis, nerve sheath myxoma, soft tissue myxoma, glial choristoma, and ossifying fibromyxoid tumor of soft parts.[4] Tumors with a chondroid element, such as cartilaginous choristoma and extraskeletal myxoid chondrosarcoma, may also come under differential diagnosis.[5] As salivary gland tissue is scarce in the anterior portion of the dorsum of the tongue, the chances of mucocele, myoepithelioma, or pleomorphic adenoma in this region are very unlikely.[4,5]

The histogenesis of the ECT remains uncertain. The immunohistochemical profile suggests that the tumor cells have some link to the neural neoplasm, but whether

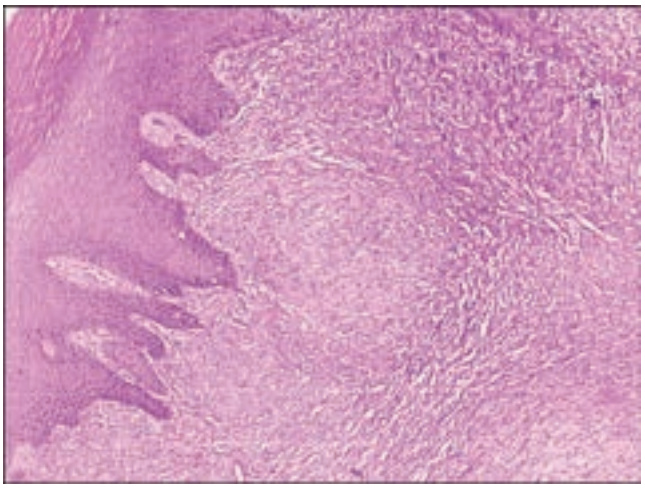

Figure 3: Cords, strands, and sheets of oval, round, fusiform bland cells, sometimes arranged in a globoid pattern (200×, hematoxylin and eosin)

the tumor cells originate directly from neural cells in the tongue or from primitive mesenchymal cells which undergo neural differentiation during tumor genesis, is still not clear.[6-10]

CONCLUSION

ECT is a rare benign mesenchymal neoplasm microscopically characterized by a biphasic myxoid and chondroid pattern. It has an excellent prognosis and a very low recurrence rate. Histologically, it should be differentiated from its mimickers. Immunohistochemical expression of S100, GFAP, and vimentin is very helpful in confirming diagnosis, suggesting a probable mesenchymal and neural origin of this rare entity.

Financial support and sponsorship

Nil.

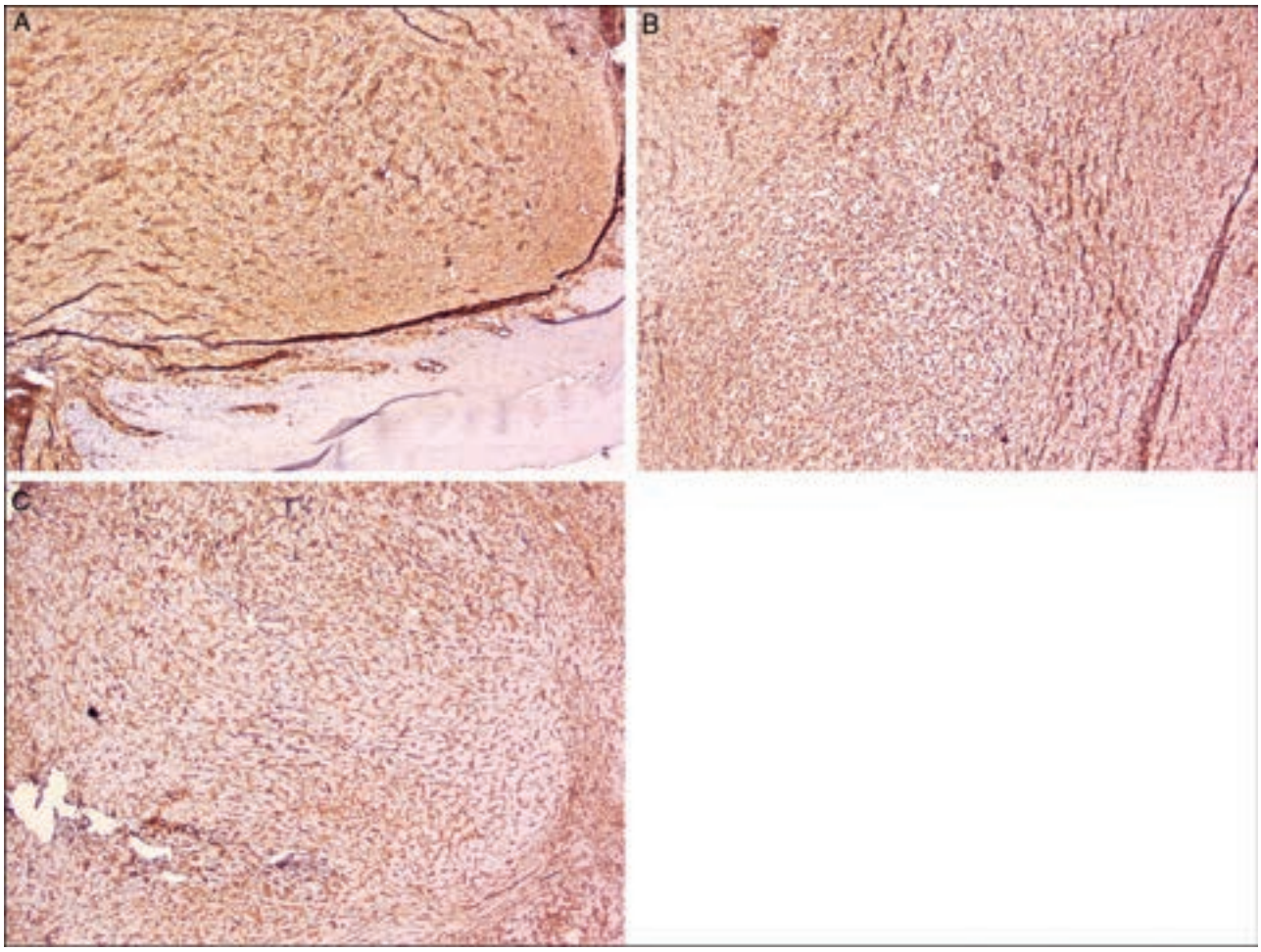

Figure 4: (A) (IHC): Tumor cells strong positive for vimentin. (B) (IHC): Tumor cells strong and diffuse positive for S-100. (C) (IHC): Tumor cells positive for GFAP

Conflicts of interest

There are no conflicts of interest.

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