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Serum sex hormone levels and red cell distribution width in type 2 diabetes mellitus

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Abstract

Red cell distribution width is a significant parameter with broad range of biological implications, variation in red cell size of subjects with type 2 diabetes can cause significant changes in sex hormones. The present study aimed to assess the serum sex hormones, red cell distribution width in type 2 diabetes mellitus compared to healthy individuals. This case–control study was performed on 100 cases (70 diabetic patients and 30 healthy individuals). The testosterone, follicle stimulating hormone and hematological indices [RBC count, hemoglobin concentration (Hb), packed cell volume (PCV), mean corpuscular volume (MCV), red cell distribution width–coefficient of variation (RDW-CV), and red cell distribution width–standard deviation (RDW-SD)] were assessed in both groups. All the analyses were performed in SPSS software (version 25). In terms of gender, the greater numbers of participants (55.7%) were female. The follicle stimulating hormone (FSH) in female diabetic patients was significantly higher than that in control group ($p < 0.001$), and the testosterone (TT) level was significantly lower in male diabetic patients ($p<0.001$). However, red cell distribution width standard deviation (RDW-SD) were increased in patients below 50 years ($p=0.040$). There were correlation between FSH, TT and RDW but not significant. The result of this study pointed out that testosterone was lower in T2DM patients while FSH was higher in T2DM patients than non-diabetes control subjects. The authors therefore, recommend that assay of sex hormones should be included in the panel of tests for T2DM during treatment.

Keywords: Follicle stimulating hormone; Diabetes; Testosterone; Red cell distribution width

1. Introduction

Diabetes is a metabolic disorder defined by hyperglycemia due to either a lack of insulin secretion, insulin resistance or both [Topaloğlu et al., 2022]. The prevalence of diabetes has risen in both developed and developing countries. This global public health disease has become a serious clinical task due to its numerous complications, rising mortality, and it's demanding high costs on the health care system [Hill-Briggs et al., 2020; Rohm et al., 2022]. Insulin resistance, a remarkable injury in persons with type 2 diabetes mellitus (T2DM), has been associated with low serum testosterone in men. Men with T2DM have been described to have significantly lower levels of serum testosterone when compared with non-diabetic men [Snyder et al., 1999; Bhasin et al., 2010; Snyder et al., 2016] along with a high prevalence of low serum testosterone ranging from 24% to 57% [Pitteloud et al., 2005; Stanworth et al., 2008]. Oh*et al.* proposed that testosterone was perhaps linked with type 2 diabetes mellitus risk. Some studies have reported that follicle stimulating hormone was associated with T2DM in males. While other studies reported that men with T2DM had lower levels of follicle stimulating hormone compared to the control group [Lakshman et al., 2010; Margulis et al., 2014; Elabbady et al., 2016]. However, some other study found that men with T2DM had increased levels of FSH than the control group [Higginset al., 2003]. Follicle stimulating hormone as a health-giving hormone, basically acts on the gonads of men, but its additional gonadal function in bones, adipose tissue, cardiovascular system and immune systems is also being demonstrated [Egger et al., 1997]. In females, high serum follicle stimulating hormones are sign of menopause and also high follicle stimulating hormones can lead to impaired glucose tolerance [DerSimonian and Laird, 1986]. Some studies

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have suggested a strong association between high serum follicle stimulating hormones levels and possibility of diabetes in postmenopausal women [Lindstedt et al., 1991; Okubo et al., 2000]. Red blood cell distribution width (RDW) is an important measure of alterations of red blood cell volume, which is assessed in the estimation and differentiation of anemia [Evans and Jehle, 1991]. High RDW is associated to an impairment of erythropoiesis, which shows chronic inflammation and oxidative stress, both of them are fundamental principle in the pathogenesis of type 2 diabetes mellitus [Dada et al., 2014]. Although, few studies reported that there was relationship between RDW and diabetes. A population-based study by Veeranna *et al*. in 2012 showed that RDW remarkably predicted glycated hemoglobin in healthy patients without diabetes. Another study in 2014 by Engström *et al*., reported that RDW was significantly and positively linked with glycated hemoglobin. It has also been proposed that red cells function as transporter of sex hormones in the bloodstream in a way closer to that of albumin, and that red cells may be in charge of delivering 5-15% of sex hormone to desired tissues [Koefoed and Brahm, 1994]. Therefore, the current study aimed to evaluate testosterone, follicle stimulating hormone and RDW in patients with type 2 diabetes mellitus.

2. Materials and Methods

2.1. Study population

The present study was performed at Enugu State University Teaching Hospital, Enugu, Nigeria, from July to November 2024. A total of 70 patients with type 2 diabetes mellitus (31 males and 39 females, aged 40–60 years) and 30 apparently healthy, non-diabetic subjects were recruited. Participants with systemic diseases; inflammatory, neoplastic and infectious diseases; heart failure, liver disease, hematological disorders (e.g., hemoglobinopathies) or cancer were excluded.

2.2. **Sample collection and laboratory analysis**

Five milliliters of blood were collected by venipuncture after overnight fast into an accurately labeled bottle for each individual. Some aliquots of the blood sample were dispensed into plain bottle for testosterone and FSH, EDTA containers for hematological indices. The blood samples for testosterone and FSH were centrifuged with a laboratory centrifuge within two hours of collection, and the serum was separated into clean, dry, plain tubes that were labeled in line with the initial blood sample bottle. The serum was then stored frozen at – 20°C and used within one week. Serum testosterone and FSH were assessed using enzyme immunoassay kit (Monobind Inc., USA) following manufacturer's instruction. Red cell indices—including RBC count, Hb, PCV, MCV, RDW-CV and RDW-SD were determined using a five-part hematology analyzer (Mindray BC 5150).

2.3. Ethical Considerations

The study was approved by the Research Ethics Committee of Enugu State University Teaching Hospital. Written informed consent was obtained from all participants.

2.4. Statistical Analysis

Statistical Package for Social Sciences version 25 was used to perform the statistical analyses. The data were expressed as mean±SD. The mean values were tested for significance using a test for paired samples. Pearson's correlation coefficients were used to determine the relationship between Testosterone, FSH and RDW. Value of $p<0.05$ was accepted as statistically significant.

3. Result

The testosterone was significantly higher in male non-diabetic control compared with diabetic patients (6.740± 1.453 ng/ml vs 3.546± 1.307, $p<0.001$ respectively). In addition, FSH was significantly higher in female diabetic patient compared with non-diabetic control (44.807 ± 10.827 mIu/ml vs 3.770 ±1.902 mIu/ml, $p<0.001$) (Table 1).

Table 1 Sex hormones and RDW of T2DM Patients vs. Controls

Subjects	TT (ng/ml)	FSH (mIU/ml)	RDW-CV (%)	RDW-SD (fl)
MP	3.546±1.307	5.043±2.047	13.826±1.287	43.590±6.250
MC	6.740±1.453	3.820±2.346	13.480±0.950	41.570±4.089
P value	<0.001	0.479	0.801	0.650
FP	0.505±0.045	44.807 ±10.827	14.525±2.083	45.767±7.086
FC	0.200 ±0.133	3.770 ±1.902	14.185±1.320	44.285 ±5.087
P value	0.001	<0.001	0.868	0.789

Abbreviation: TT=Testosterone, MP= male patient, MC=male control, FP=female patients, FC=female control

The testosterone was significantly higher in male T2DM patients compared with female diabetic patients (3.266± 0.996 ng/ml vs 0.422± 0.203ng/ml, p<0.001 respectively). In addition, FSH was significantly higher in female diabetic patient compared with male diabetic patients (46.120 ± 8.419 mIu/ml vs 5.336 ±1.706 mIu/ml, p<0.001 respectively) (Table 2).

Table 2 Gender comparison of sex hormones and RDW

Parameters	Female (N=39)	Male (N=31)	p-value
Testosterone (ng/ml)	0.422 ± 0.203	3.266 ± 0.996	<0.001**
FSH (mIU/ml)	46.120 ± 8.419	5.336 ± 1.705	<0.001**
RDW-CV (%)	14.525 ± 2.033	13.826 ± 1.237	0.203
RDW-SD (fl)	45.767 ± 7.056	43.598 ± 6.250	0.365

The RDW-SD was significantly higher in T2DM patients between 30-49 years compared with T2DM diabetic patients between 50-69 years (46.782± 7.845 fl vs 42.885± 4.844 fl, p=0.040 respectively) (Table 3).

Table 3 Comparison of sex hormones and red cell indices based on age

Parameters	30-49 years (N=35)	50-69 years (N=35)	p-value
Testosterone (ng/ml)	1.517 ± 0.543	1.765 ± 0.599	0.786
FSH (mIU/ml)	29.988 ± 20.170	27.294 ± 22.623	0.859
FBS (mmol/L)	6.662 ± 1.106	6.962 ± 1.007	0.466
RBC count (1012/L)	4.065 ± 0.729	4.386 ± 0.571	0.108
HGB (g/dl)	11.780 ± 2.376	12.842 ± 1.891	0.104
PCV (%)	35.282 ± 7.156	38.494 ± 5.696	0.103
MCV (fl)	86.897 ± 9.878	87.834 ± 8.241	0.903
RDW-CV (%)	14.682 ± 1.772	13.585 ± 1.260	0.109
RDW-SD (fl)	46.782 ± 7.845	42.885 ± 4.844	0.040*

Red cell indices correlated with both FSH and testosterone but not significant (p>0.05). Fasting blood sugar significantly correlated negatively with FSH and positively with testosterone (p<0.05) (Table 4).

Table 4 Pearson's correlations (r) of red cell indices with testosterone and FSH among T2DM patients

Parameters	FSH r (p-value)	Testosterone r (p-value)
RDW-CV	0.144 (0.234)	-0.217 (0.071)
RDW-SD	0.095 (0.434)	-0.146 (0.228)
FBS	-0.363 (0.002)*	0.356 (0.003)*
RBC	0.011 (0.926)	0.049 (0.686)
HGB	-0.002 (0.988)	0.094 (0.540)
MCV	-0.007 (0.952)	0.069 (0.571)

Figure 1 shows that 55.7% of the patients are female while 44.3% are male. Fifty percent of the patients were between 30-49 years and the remaining 50% were between 50-69years

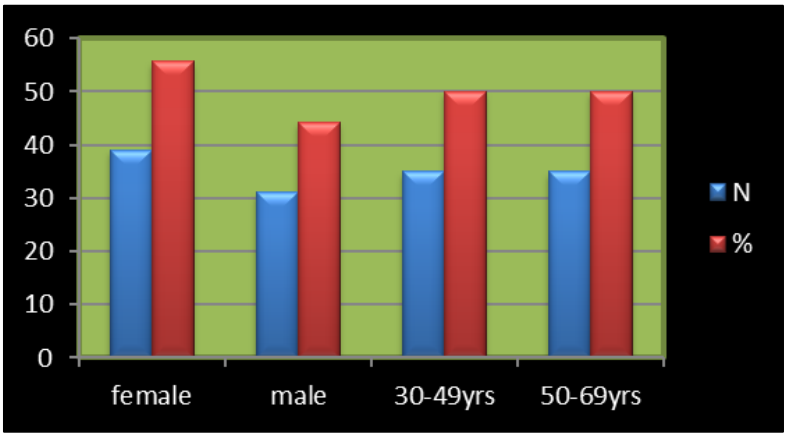

Figure 1 Gender and age range

4. Discussion

Our study investigated the serum level of testosterone, FSH and RDW in T2DM and compared it with apparently healthy non-diabetes mellitus subjects. Previous studies have suggested that testosterone has an important protective effect against T2DM among men, and men with increased testosterone level have a lower risk for T2DM than those with decreased testosterone level [Stellato et al., 2000; Rosmond et al., 2003; Kameda et al., 2005]. The findings of this study indicate that serum testosterone levels were decreased in male patients with T2DM compared with non-diabetic controls. This is similar to a previous study done in Nigeria men with T2DM which reported that calculated free testosterone (CFT) levels of men with T2DM was significantly lower than that of the non-diabetic controls [Ngamariju et al., 2021]. Some hypotheses have been proposed to clarify the association between testosterone and diabetes [Rao et al., 2013; Grossmann, 2014]. Earlier studies have demonstrated the inverse association between testosterone and insulin resistance, and persons with testosterone deficiency have increased level of insulin resistance, which can likewise result in increased chances of T2DM [Tsai et al., 2004; Yeap et al., 2009]. Previous studies have provided strong evidence that serum FSH levels are lower in men diagnosed with T2DM. Some other studies have also found that the high FSH levels usually occurred in postmenopausal women and it induces glucose intolerance [Rezvani et al., 2012; Cheng et al., 2023]. In our study, FSH in female T2DM patients was 10-fold higher than the non-diabetic control subjects. This study completely agreed with previous study done by Liu *et al*., which observed serum follicle stimulating hormone levels in postmenopausal females were approximately 10-fold higher than those in their pre-menopausal counterparts. Serum follicle stimulating hormone levels undergo surprising changes with age due to the absence of negative feedback from inhibin, along with androgens and estrogens, in elderly males and females, respectively [Feldman et al., 2002; Ausmanas et al., 2007; Araujo and Wittert, 2011]. In females, increase serum follicle stimulating hormone levels are one of the diagnostic signs of menopause [Davis et al., 2015]. Red cell distribution width is inexpensive test, freely available and it has significant correlation with glycated hemoglobin [Bhutto et al., 2019]. Slight increase in RDW of patients between 30-49 years was observed in present study. Previous studies have reported that a high RDW increases the

levels of oxidative stress and show chronic inflammation, both of them suggesting type 2 diabetes mellitus, which may lead to the development of atherosclerotic diseases [King and Loeken, 2004; Knapp et al., 2019]. Meanwhile, a review study by Abyaza and Shirali reported the efficacy of red cell distribution width as a prognostic marker for diabetes. Finally the present study needs further studies with larger sample size to validate the findings.

5. Conclusion

The result of this study pointed out that testosterone was lower in T2DM patients while FSH was higher in T2DM patients than those without diabetes. The authors therefore, recommend that assay of sex hormones should be included in the panel of tests for T2DM during treatment.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declared that no competing interests exist.

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This research did not receive any specific grant from any funding agency in the public, Commercial, or non-profit organizations.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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