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Research Article

Study to evaluate serum free testosterone and hsCRP concentration to predict low hematocrit in type 2 diabetes mellitus

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ABSTRACT

Background: The primary objective of the study was to assess serum free testosterone and high sensitivity c-reactive protein concentrations and their correlation with hematocrit in patients of diabetes mellitus type 2. Hypogonadotropic hypogonadism is a common defect in type 2 diabetes, irrespective of the glycemic control, duration of disease, and the presence of complications of diabetes or obesity. It has been demonstrated that about one third of male patients with diabetes mellitus type 2 have low serum free Testosterone level.
Methods: We have included 50 patients of diabetes mellitus type 2 presenting to the department of medicine SMS Hospital Jaipur. Both indoor and out door patients were selected who were free of microalbuminuria and diabetic nephropathy. Primary or secondary hypogonadism, other than diabetes mellitus and anemia of other causes were ruled out.
Results: Diabetes mellitus type 2 patients with low serum free testosterone levels have significantly low hematocrit values (n= 29) (p-value <0.001) and mild anemia compared to eugonadal men (n= 21). Their correlation was highly significant. Patients with DM type 2 who have low serum free testosterone, also have high hs-CRP concentration. Though hematocrit values were low in patients with high hs-CRP concentration but it was not statistically significant.
Conclusion: At the end of the study we concluded that both a low serum free testosterone level and high hs-CRP concentration may play an important role in the pathogenesis of mild anemia and low hematocrit values in DM type 2 patients.

Keywords: Type 2 diabetes mellitus, Serum free testosterone levels, hs-CRP concentration, Hematocrit

INTRODUCTION

Diabetes Mellitus type 2 is a very common metabolic disorder in India, and it has been said the "Diabetic Capital of the world".[1] Diabetes mellitus itself leads to a variety of complications affecting all major systems of the body.

It has been demonstrated that about one third of male patients with diabetes mellitus type 2 have low serum free Testosterone level. Low serum testosterone level is also associated with high c-reactive protein levels which is a marker of ongoing systemic inflammation.[2]

The male diabetic patients who have low free serum Testosterone level and high c-reactive protein levels have an association with low hematocrit and a frequent occurrence of mild normochromic normocytic anemia. Testosterone is known to stimulate the proliferation of erythroid progenitors, largely by erythropoietin-independent mechanisms. This function may be particularly important in the setting of diabetes, where the

uncoupling of erythropoietin synthesis from Hb levels may require the integrity of such pathways to maintain Hb levels.[3] Thus low free testosterone & chronic inflammatory mechanisms may contribute to mild anemia in diabetic patients.[4]

Such patients may also have a high risk of atherosclerotic cardiovascular events in view of their markedly elevated high sensitivity c-reactive protein concentration, specially in diabetic patients.[2]

METHODS

We have included 50 patients of diabetes mellitus type 2 presenting to the department of medicine SMS Hospital Jaipur. Both indoor and outdoor patients were selected. Selection was based on the Inclusion & Exclusion criteria cited below.

I. Inclusion Criteria

- Diagnosed male patients of Diabetes mellitus type 2 above the age of 18 years.

II. Exclusion Criteria

Patients with microalbuminuria, diabetic nephropathy, patients with known history of Primary or Secondary hypogonadism other than type 2 DM, patients of hypopituitarism, patients of renal failure, patients of cirrhotic liver disease, patients on steroid therapy, patients of HIV serology positive and patients with other causes of anemia e.g. Iron deficiency, vit. B_{12} & folate deficiency were excluded.

Serum free testosterone levels was measured in specialised laboratory for hormonal assays, by the analog free testosterone assay method, which is a rapid, simple and easily reproducible method of free testosterone estimation.[5] Normal range was 1-8.5 ng/dl (10-85 pg/ml). Lower tercile i.e. below 3.5 ng/dL was considered as low and the subject was defined hypogonadal.

LH (luteinising hormone) & FSH (follicle stimulating hormone) was measured by chemiluminescent immunometric assay (CLIA) method. Normal range was 2-12 mIU/ml for LH & 1-12mIU/ml for FSH in adult men. Hypogonadotrophic state was defined as inappropriately low FSH and LH concentrations for the concomitant subnormal free testosterone concentrations. Thus, LH and FSH concentrations in the normal reference range would be considered to be "low" when associated with low serum free testosterone concentrations.[2]

While C-reactive protein levels was measured by using a high sensitivity enzyme linked immunosorbant Assay kit. hsCRP levels >3 mg/l were termed "high" because those concentrations are known to be associated with increased cardiovascular events.[6] Data are presented as means ± standard errors. Students t-test is used to compare parametric data. Fishers exact test and x^2 test are used to compare groups wherever applicable. P Value of <0.05 has been considered significant. Pearson's formula is utilised for correlation.

RESULTS

Diabetes mellitus type 2 patients with low serum free testosterone levels have significantly low hematocrit values (37.28 ± 1.91) (n = 29) and mild anemia compared to eugonadal men (41.18 ± 1.99) (n = 21). This correlation was highly significant (p-value <0.001). Patients with DM type 2 who have low serum free testosterone, also have high hs-CRP concentration. Though hematocrit values were low (38.32 ± 2.62) in patients with high hs-CRP concentration (n = 35) and higher (40.82 ± 2.19) in patients with low hs-CRP concentration (n = 15) but it was not statistically significant (p value < 0.05). Thus both a low serum free testosterone level and high hs-CRP concentration may play an important role in the pathogenesis of mild anemia and low hematocrit values in DM type 2 patients.

DISCUSSION

Anemia in diabetes mellitus type 2 is multifactorial.[7,8] In a country like India, where nutritional causes of anemia are common. We screened out lot of patients, which were having identifiable causes of anemia e.g. iron deficiency anemia, B_{12} deficiency and folate deficiency anemia. Present study was conducted in the department of medicine, SMS medical college and hospital Jaipur. We found many difficulties in case selection. Diabetic patients in India are usually presenting late to the health care system, by the time they are having many complications. Many patients with newly diagnosed DM type-2, were having microalbuminuria at presentation and excluded from the study. Erythropoietin is normal or elevated in early DM type 2 who have mild anemia, before the onset of established nephropathy. But there is inappropriately decreased reticulocyte response to erythropoietin.[9]

There are many papers published and lot of research work has been done on androgen status and diabetes. Testosterone levels are low in diabetic population. The relation between testosterone and anemia is well established and supported by many studies.[10,11,12] Serum free testosterone values depend upon the method of measurement.[13,14] It is classified low, if it falls in the lowest tercile or quartile in the normal range according to different authors. E Selvin et al[8] considered lowest tercile of free and bioavailable testosterone as low testosterone. S. Dhindsa et al[4] considered lowest quartile for bioavailable testosterone. They used vermulen formula to calculate free testosterone. In our study we used "analog free testosterone assay" method in our study[15] and considered the lowest tercile as low free testosterone and the patients in this group are termed hypogonadal.

In our study, the mean hematocrit in hypogonadal men was 37.28 ± 1.91 and it was 41.18 ± 1.99 in eugonadal men. This observation shows that hypogonadal DM type 2 men have significantly lower hematocrit than eugonadal men (Table 1). Vishal Bhatia et al[2] supported that 37 patients in their study were hypogonadal and had significantly lower hematocrit (40.6 ± 1.1) than eugonadal men (43.3 ± 0.7). It was also supported by Luigi Ferrucci et.al[11] and they found that older individuals with low testosterone were anemic as compared to normal testosterone levels.

Table 1: Mean ± SD of hematocrit according to free testosterone of the subjects.

Parameter	Free testosterone		P. Value	Significance
	≤ 3.5 ng/dL	> 3.5 ng/dL		
Hematocrit	37.28 ± 1.91	41.18 ± 1.99	<0.001	Highly significant

In this study, serum free testosterone levels were significantly lower in patients with high hsCRP concentration (p-value is <0.001). Similarly table no. shows that hsCRP concentrations were higher (19.64 ± 19.68) in hypogonadal men. This observation was supported by Dhindsa et al[4] and V. Bhatia et al.[2] It means that chronic inflammation may lead to low testosterone levels and its consequences like low hematocrit values.

Though the hematocrit was lower (38.32 ± 2.62) in patients with elevated hsCRP > 3mg/L, while it was higher (40.82 ± 2.19) in patients with hsCRP less than 3mg/L. It was not statistically significant (p-value > .05) in our study (Table 2). Vishal Bhatia et al.[2] showed that hematocrit was significantly lower in DM type 2 patients who have elevated CRP concentration.

Table 2: Mean ± SD of hematocrit according to hsCRP of the subjects.

Parameter	hsCRP		P-value	Significant
	< 3 mg/L	≥ 3 mg/L		
Hematocrit	40.82 ± 2.19	38.32 ± 2.62	< .05	

Table 3: Mean ± SD of hsCRP of the subjects according to cut off value of free testosterone.

	Free testosterone		P-value	Significance
	≤ 3.5 ng/dL	> 3.5 ng/dL		
Mean ± SD (hsCRP)	19.64 ± 19.68	4.17 ± 3.25	< .001	Significant

We established correlation between serum free testosterone level, hsCRP concentration and hematocrit.

We found that Serum hsCRP concentration and hematocrit are negatively correlated (r = –0.556).

Table 4: Correlation between hsCRP v/s hematocrit and free testosterone v/s hematocrit.

Correlation	r-value	P-value	Significance
hsCRP v/s Hematocrit	-0.556	< .001	Highly Significant
Free testosterone v/s Hematocrit	+ 0.694	< .001	Highly Significant

Means that when hsCRP increases Hematocrit decreases (p- value <0.001). Serum free testosterone level and Hematocrit have positive correlation (r = +0.694) meaning that when free testosterone increases within normal range, Hematocrit also increases (p- value <0.001). Both the correlations are highly significant.

CONCLUSION

At the end of the study we concluded that hypogonadotrophic hypogonadism is common in middle aged patients with diabetes mellitus type 2 in our population and their serum free testosterone levels are low. Diabetes mellitus type 2 patients with low serum free testosterone levels have significantly low hematocrit values (p-value <0.001) and mild anemia compared to eugonadal men. Their correlation was highly significant. Patients with DM type 2 who have low serum free testosterone, also have high hs-CRP concentration. Though hematocrit values are low in patients with high hs-CRP concentration but it was not statistically significant.

Thus both a low serum free testosterone level and high hs-CRP concentration may play an important role in the pathogenesis of mild anemia and low hematocrit values in DM type 2 patients.

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