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Gender as Risk Factor for Thyroid Dysfunction in Patients with Type-II Diabetes Mellitus; A Retrospective Analysis in a Cohort Located at Lahore, Punjab, Pakistan

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Author`s Contribution

[A] Conception and design, Collection and assembly of data, [T]Analysis and interpretation of the data, Statistical expertise, [A,T]Final approval and guarantor of the article

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A B S T R A C T

Introduction: Type II diabetes mellitus (DM) is the most common endocrine disorder. It has been reported that type II DM has been associated with thyroid dysfunction that make Methodologydifficult in maintain metabolic homeostasis later in life.

Methodology: Total 300 study participants were included in this retrospective study. The individuals were investigated for blood sugar fasting (BSF), HBA1C performed on automated analyser Architect CI 8200 and thyroid stimulating hormone (TSH), freeT4, T3 on automated immunoassay analyser Cobas-e411.

Results: One fifty-two (50.67%) out of total 300 were diagnosed with diabetes and 148 (49.34%) were grouped as non-diabetic. Total 101 out of 152 diabetic patients were females among them 14 (13.86%) were observed with hypothyroidism and 14 (13.86%) with hyperthyroidism (p-value 0.000). No significant results were observed in the male group.

Conclusion: Thyroid dysfunction is observed more significantly in females' diabetic patients. Thyroid hormone imbalance occurs considerably among diabetic females that make difficult to maintain the glucose level. Diabetic patients must be regularly evaluated for thyroid profile on regular intervals. Managing both of these endocrinal disorders will increase the efficiency of diabetic treatment and may decrease in the morbidity rate.

Keywords: Diabetes mellitus, endocrine disorder, Thyroid dysfunction, HBA1C, Hyperglycaemia,

Introduction

Diabetes is a set of metabolic disorder.[1] Lack of insulin may result in impaired metabolism of starches, proteins and fat metabolism.[2] Diabetes has two major types including Type-1 and Type-2 diabetes.[3] Type-2 diabetes is a multifactorial disease with innate qualities linked with resistance to insulin and also impeded secretion of insulin. Ecological components and individual habitual behaviour like obesity stress , over eating, nonappearance of physical exercise and aging are prime factor of type 2 diabetes.[4] Type-2 diabetes includes solid relationship with hereditary qualities somebody obtain from family. In monozygotic twins the recurrence of Type-2 diabetes is much more than dizygotic twins showing hereditary variables involvement.[5] Multiple genes like mitochondrial genes insulin receptor genes and glucokinase genes are recognized as associated with causing type 2 diabetes if not transcribed completely. A mutation in KCNQ1 gene which is engaged with secretion of insulin is recognized in Asian population for its relationship with pathogenesis of type 2 diabetes.[6] Instances of Type-2 diabetes are recognized to be related with hereditary roots showing hugeness of attributes we get from ancestors.[5]

The obesity initiates resistance to insulin and results in progression of Type-2 diabetes in patients with middle age and in old age people. Numerous variables are related with expanded fat aggregation in body and this accumulation of fat results in resistance to insulin. These components incorporate

excessive eating of sugars, diminished exercise propensity, alcohol utilization, smoking propensity, nervous system issue, raised cortisol level, imbalance of sex hormones, older age, and hereditary reasons.[7] Pathophysiology involved withType-2 diabetes is equally attributed by resistance to insulin as well as its impaired production. Postprandial hyperglycaemia, impeded glucose resistance during glucose tolerance test (GTT) and reduction of insulin secretion in early period of ailment is a fundamental pathophysiological occasion during beginning of diabetes. Different genes related with visceral obesity like uncoupling protein (UCP) gene and β3 AR (adrenergic receptor) gene are additionally connected with improvement of resistance to insulin.[9] Different variables like inflammation mediators and glucolipotoxicity assume their job in signalling debilitation of insulin and insulin secretion defect.[10] Thyroid hormones are secreting from thyroid organs. The name thyroid organ was signified first time in 1965 by Thomas Wharton .[11] In nineteenth century Robert Graves proposed thyrotoxicosis first time in a female patient of goiter, gave increased heartbeat and exophthalmos. Additionally hypothyroidism was likewise perceived as a syndrome in same century.[12] Thyroid hormones direct numerous metabolic processes and apply pleotropic impacts on numerous organs. The thyroid organ under stimulus of TSH (Thyroid stimulating hormone) incorporate and secreteT3(Tri-iodothyronine) and thyroxine (T4), the sole hormones in people contain iodine. The greater part of the discharged T3 and T4 bound with proteins like T4-restricting globulin, transthyretin and albumin however this coupling can be separate quickly if necessary. The amalgamation of thyroid hormones is interceded by thyroid stimulating hormone (TSH) which is also called thyrotropin, blended in anterior part of pituitary gland by stimulus of TSH releasing hormone (TRH) produced in hypothalamus. Free T3 and Free T4 create negative feedback and stops the release of Thyroid stimulating hormone (TSH) and TSH releasing hormone (TRH) to continue the enhanced dimension of thyroid hormones in blood.[13] Coller and Huggins in 1927 initially revealed the relationship among hyperthyroidism and diabetes. As indicated by them diabetes gets exacerbate by the hyperthyroidism condition and thyroidectomy improves glucose resistance in diabetic patients experiencing hyperthyroidism.[14] Diabetes mellitus has significant connection with thyroid dysfunction. Autoimmunity is the main source of thyroid dysfunction (TD) in patients with diabetes.[15] The association between TD and type 2 diabetes mellitus is a less engaged zone which may answer numerous inquiries identified with metabolic disorder like hypertension, atherosclerosis and related cardiovascular ailments.[16] Thyroid Hormones are accounted for to coordinate discharge of insulin from β cells of pancreas. Hypothyroidism is related with lessened emission of insulin from pancreas while hyperthyroidism results in expanded mass of β cells. Thyrotoxicosis likewise causes raised insulin clearance.[17] Hyperthyroidism otherwise called thyrotoxicosis is the condition in which abundance thyroid hormones (T3 and T4) are delivered while dimension of TSH is underneath than ordinary on account of raised dimensions of thyroid hormones. Thyrotoxicosis results in expanded yield of glucose from liver on account of upgraded glycogenolysis. This expanded glucose yield causes hyper-insulinaemia, glucose in tolerance and peripheral resistance of insulin.[18] Hypothyroidism is the condition portrayed by diminished production of thyroid hormones went with raised dimensions of Thyroid stimulating hormone (TSH). Hypothyroidism prompts diminished assimilation of glucose from gastrointestinal tract, aggregation of peripheral glucose, gluconeogenesis diminishes yield of glucose from liver and diminished glucose disposal. In either subclinical or overt hypothyroidism insulin resistance causes secretion of insulin stimulated by presence of glucose.[16] Hypothyroidism (Subclinical) additionally causes decreased glucose transport (insulin interceded) as a result of translocation of glucose transporter type 2 gene (GLUT-2) which causes its modified articulation and create insulin obstruction.[19] The increase of diabetes prevalence in adult population is not ignorable, an alarming situation for health care authorities. The latest figures from the International Diabetes Federation (IDF) indicate that as of 2015 more than 415 million people worldwide have diabetes[20] This number is expected to increase to 642 million by 2040.[21] Forty-three percent of these 3.7 million deaths occur before the age of 70 years. The percentage of deaths attributable to high blood glucose or diabetes that occurs prior to age 70 is higher in low- and middle-income countries than in high-income countries.[22]

Pakistan still facing diabetes mellitus as an emerging health care problem and its morbidity and mortality is still on the rise. Despite all progress in field of medical sciences diabetes still remains an incurable and persistent disease in the world. Early diagnosis of diabetes is important for a better living standard as late diagnosis of ongoing diabetes in any undiagnosed patient may result is worse consequences.

Methodology

A retrospective study was designed at the Department of Medical Laboratory Sciences, University of Lahore. Total 300 subjects were recruited in this study on following criteria. Study participants were screened for diabetic and non-diabetic according to the WHO criteria (70-126 mg/dl are Normal and more than 126 mg/dl are diabetic). The focused age group in both cases and controls were the individuals having 20-70 years of age. Both males and females were

included in this study. Subjects without any serious complications, performing normal daily activities were incorporated in study. The exclusion criteria were made on the basis of the subjects such as; subjects less than 20 years or above 70 years of age individual with past history of TD (Thyroid Disease), persons using drugs such as thyroxine, and thyroid drugs, glucocorticoids and oral contraceptives, patients suffering from other diseases i.e. hepatobiliary diseases, patients on dialysis and pregnant women were also excluded from this study.

Estimation of Blood sugar fasting, HbA1C and Thyroid function test

Blood sugar fasting level were performed after fasting of 10 to 12 hours and sample were collected in sodium fluoride vial by using standard venous puncture technique. Fresh sample for HbA1C were collected in EDTA vial. For thyroid function test, blood sample was collected in gel vacutainer without additive and serum was separated by centrifugation. Fasting blood sugar level was performed by kits (Abbott diagnostics) using fully automated analyzer Architect CI 8200. Thyroid Stimulating Hormone estimation, T3, T4 level was done by using fully automated immunoassay analyzer Cobas-e411 using kits provided by Roche diagnostic. HBA1c estimation was performed by kits (Abbott diagnostics) using fully automated analyzer Architect CI 8200. Data was analysed by SPSS version 24.0. Categorical variable was expressed as frequencies and percentages whereas continuous variables were expressed as mean ± S.D. Chi-square test, Pearson correlation and Independent samples t-test were used to analyze data. *P-value*≤ 0.05 was considered as statistically significant.

Results

A total sample of 300 patients were included in the study, from which 93 (31%) were males and 207(69%) were females. Study subjects were divided in two groups, one included all the diabetic patients (Cases) and the other was non-diabetic patients (Controls). Total diabetic patients were 152 (50.67%) and from these groups the male diabetic patients were 51(17%) and the female diabetic patients were 101(33.67%) in figure 1. The total non-diabetic patients were 148(49.33%) whereas the male non-diabetic patients were 42(14%) and the females were 106(35.33%).

Study subjects were age wise divided into 5 groups (figure 2). Result found the number of individuals 8 (2.7%), 14 (4.7%), 16 (5.3%) were included in Group 1 (20-29 years) Group 2 (30-39 years) and in Group 3 (40-49 years) respectively. There were 113 (37.3%) numbers of individuals included in Group 4 (50 to 59 years) and found the total 149 (49.7%) with the age of more than 60 years.

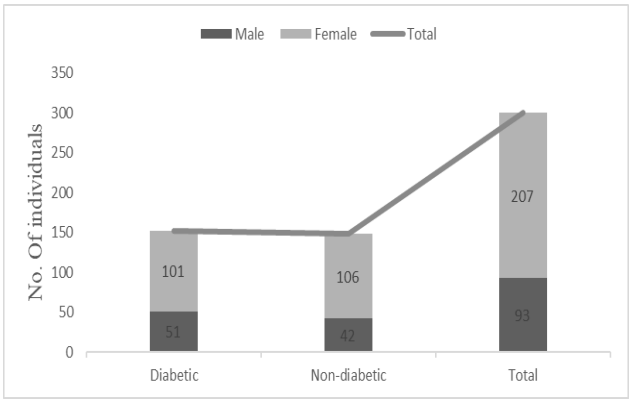

Figure 1. Distribution of Diabetic and Non-Diabetic Study Population

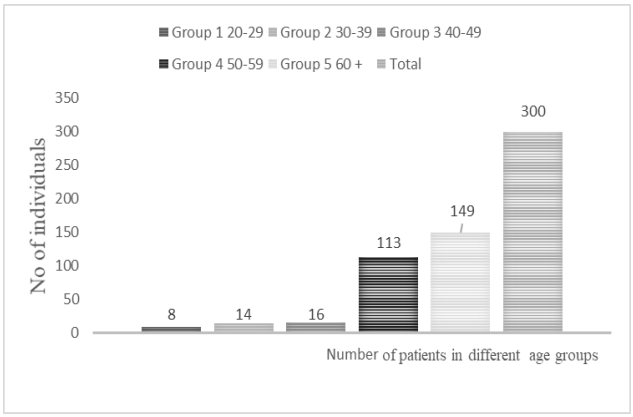

Figure 2: Age wise distribution of study subject

Mean TSH value of female diabetic patients was 3.22±7.38 and non-diabetic patients was 3.38±9.93 (*p-value* 0.817) whereas mean TSH of male diabetic patient was 2.65±1.74 and non-diabetic was 1.86±1.65(*p-value* 0.035). Mean T3 female diabetic patient was 2.07±0.79 and non-diabetic patients was 2.10±0.84 (p-value 0.229). Mean T3 male diabetic patient was 2.05±0.44 and non-diabetic patients was 2.10±1.29(p-value 0.241). Mean FT4 female diabetic patient was19.43 ±9.36 and non-diabetic patients was 16.38±9.18 (p-value 0.002). Mean FT4 male diabetic patient was 19.18±5.76 and non-diabetic patients was 18.64±13.14 (*p-value 0.0758*). Mean BSF of female diabetic was 180±59.46 and non-diabetic was 100.24±10.27. Mean BSF in male diabetic was 182.78±63.07 and in non-diabetic was 101.12±10.34. Mean HBA1c of female diabetic patient was 7.96±2.07 and non-diabetic was 5.11±0.35. Mean HBA1c of male diabetic patient was 7.91±2.24 and non-diabetic was 5.15±0.36 (table I).

Table I: Mean±SD values of thyroid and diabetes test in both genders

	Female					Male				
	Diabetic	Mean±SD	Non-diabetic	Mean±SD	*p-value (< 0.005)*	Diabetic	Mean±SD	Non-diabetic	Mean±SD	*p-value (< 0.005)*
TSH	101	3.22±7.38	106	3.38±9.93	0.817	51	2.65±1.74	42	1.86±1.65	0.035
T3	101	2.07±0.79	106	2.10±0.84	0.229	51	2.05±0.44	42	2.10±1.29	0.241
FT4	101	19.43±9.36	106	16.38±9.18	0.002	51	19.18±5.76	42	18.64±13.14	0.758
BSF	101	180±59.46	106	100.24±10.27	0.000	51	182.78±63.07	42	101.12±10.34	0.000
HBA1c	101	7.96±2.07	106	5.11±0.35	0.000	51	7.91±2.24	42	5.15±0.36	0.000

Table II. Number of Diabetic and non-diabetic individuals with analysis of thyroid and diabetes test in both genders

		Female					Male				
Parameter	**Values**	**Diabetic**	**Non diabetic**	**Total**	**Percentage (%)**	**p-value**	**Diabetic**	**Non diabetic**	**Total**	**Percentage (%)**	**p-value**
BSF	Low	0	0	0	0	0.000	0	0	0	0	0.000
	Normal	2	106	108	52.2		1	42	43	46.23	
	High	99	0	99	47.8		50	0	50	53.77	
	Total	101	106	207	100		51	42	93	100	
HBA1c	Low	0	0	0	0	0.000	0	0	0	0	0.000
	Normal	1	106	107	51.69		1	42	43	46.23	
	High	100	0	100	48.31		50	0	50	53.77	
	Total	101	106	207	100		51	42	93	100	
TSH	Low	19	7	26	12.56	0.006	3	5	8	8.60	0.325
	Normal	67	90	157	75.85		44	36	80	86	
	High	15	9	24	11.59		4	1	5	5.40	
	Total	101	106	207	100		51	42	93	100	
FT4	Low	14	3	17	8.21	0.000	1	0	1	1	0.600
	Normal	73	99	172	83		48	41	89	95	
	High	14	4	18	8.70		2	1	3	3.2	
	Total	101	106	207	100		51	42	93	100	
T3	Low	14	2	16	7.72	0.000	0	0	0	0	0.889
	Normal	76	100	176	85		50	41	91	97.84	
	High	11	4	15	7.24		1	1	2	2.15	
	Total	101	106	207	100		51	42	93	100	

In female diabetic group 2(1.98%) had normal, and 99(98.02%) had high BSF level out of 101. All the 106(100%) non-diabetic females had normal fasting blood glucose (p-value 0.000). In male diabetic group 1(1.96%) subject was normal,

and 50(98.04%) were high in BSF out of 51 subjects. In non-diabetic male group, all of the 42(100%) individuals had a normal BSF level (p-value 0.000).

Out of 101 female diabetic patients 1(0.99%) was normal, and 100(99.01%) were high for HbA1c, in the non-diabetic group all the 106(100%) individuals had a normal HbA1c (p-value 0.000). in the male diabetic group 1(1.96%) was normal, and 50(98.04%) had a high HbA1c level. In non-diabetic male group out of all the 42(100%) individuals had a normal HbA1c value (p-value 0.000). Total 19(18.81%) patients had low TSH level, 15(14.85%) had a high level of TSH and 67(66.34%) were normal out of total 101 diabetic females, while out of 106 non-diabetic females 7(6.6%) had a low TSH, 9(8.49%) had high TSH, and 90(84.9%) were normal in TSH level respectively (p-value 0.006). In the male group 51diabetics were enrolled out of which 3(5.8%) were low, 4(7.84%) were high, and 44(86%) had a normal TSH. Out of 42 non-diabetic 5(11.9%) were low, 1(2.38%) were high, and 36(85.71%) were normal in their TSH levels respectively (p-value 0.326). Fourteen (13.86%) out of 101 diabetics females had a low, 14(13.86%) had a high, and 73(72.28%) had a normal FT4 value. In non-diabetic group 3(2.83%) were low, 4(3.77%) were high and 99(93.39%) had a normal FT4 level respectively out of 106(p-value 0.000). In male out of 51 diabetic males 1(1.9%) was low, 23.92%) were high, and 48(94.12%) were normal in FT4 level correspondingly, while in non-diabetic group 1(1.07%) was low, 3(3.23%) were high, and 89(95.69%) were normal for FT4 out of 93 subjects (p-value 0.600) (Table II).

Fourteen (13.86) out of total 101 diabetic females had a low, 11(10.89%) had a high, and 76(75.24%) had a normal T3 level correspondingly. In non-diabetic group 2(1.88%) were low,

4(3.77%) were high, and 100(94.34%) were normal with their T3 levels respectively out of 106 individuals (p-value 0.000). In the male group out of 51 diabetics, 0 patients had low, 1(1.96%) had high and 50(98.03%) subjects had a normal T3 level respectively. In non-diabetic group 0 individuals had low T3, 1(2.38%) had high T3 level and 41(97.62%) had normal value of T3 out of total 42 subjects (p-value 0.889) (Table II).

Discussion

Diabetes mellitus is a composite and multifactorial diseases and it causes collateral damage to many other organ systems.[23] Diabetes mellitus and thyroid abnormities are the two commonly encountered diseases in the fields of endocrinology and metabolism, and their concurrence is frequently recorded. Literature-based on evidence reports that type 2 diabetes mellitus has an interconnecting fundamental pathology with thyroid dysfunction, by meddling with metabolic pathways and through autoimmunity. Both hypothyroidism and hyperthyroidism are ought to induce insulin resistance and escalate complication occurring in diabetes militias.[24,25]

The current study has reviled a significant effect of diabetes on thyroid function in female patients. Nineteen (18.81%) out of 101 female diabetic patients had low levels of TSH and 15(14.85%) (statistical significance p< 0.006) had high levels of TSH. Similarly, 14(13.86%) diabetic females were low in T3 level and 11(10.89%) were above the upper normal limit respectively (statistical significance p< 0.000). 14(13.86%) female of the diabetic group was low in T4 and 14(13.86%) were categorized in hyperthyroidism (statistical significance p<0.000). No significant correlation was observed in the male group. Present study established that out of 101 female diabetic patients 14(13.86%%) and 14(13.86%) were with hypothyroidism and hyperthyroidism respectively. Females are at a greater risk of developing thyroid dysfunction because of the autoimmune nature of the disease, in fact, the risk is 7 times greater in contrast to males.[25] The current study coincides with the report published by Manjunath. SC et al, they reported hypothyroidism in 13% of diabetic patients.[26] A study conducted at Jordan has reported that thyroid dysfunction was present in 12% of type 2 diabetes mellitus patients.[14] Palma et al have confirmed that 14.7% of diabetic patients were having thyroid dysfunction, and 10.8% of patients were positive for anti-TPO antibodies.[27] Distiller LA et al randomly surveyed 922 diabetics for thyroid dysfunction, their finds are comparable to present work, they discovered that 11.8% diabetics had a thyroid abnormality, Moreover, the findings exhibited a higher percentage of thyroid dysfunction in females than males, 5.4%, and 22.5% correspondingly.[28] A lower number of diabetics with thyroid dysfunction then current work are observed in the Japanese population, were 8.7% diabetics had subclinical hypothyroidism. Similar results were presented by a study conducted in Taiwan, which conforms 6.3% of diabetic subjects were diagnosed with subclinical hypothyroidism.[29] A recent study states that out of 364 diabetic patients, 9.9% of subjects had thyroid dysfunction, out of a total of 7.59% and 2.31% had hypothyroidism and hyperthyroidism respectively.[30] On the contrary higher number of subjects with thyroid fluctuations among diabetics, than current study was presented by Yasuda, T et al in Japan argued that out of 159 studied diabetic patients, 17% had hypothyroidism.[31] Higher frequency of thyroid dysfunction is also interpreted in a research paper from Germany where authors state that 27.3% diabetics showed thyroid imbalance, out of which 62.2% were females.[32] Correspondingly Alam, MJ et al, in their paper claims that 18.6% and 11.4% diabetics enrolled in the study were with hypothyroidism and hyperthyroidism, more than the present study. Authors also noticed that women are more likely to be engaged in thyroid anomalies as compared to the males.[33] Reports from Nigeria and India illustrates high percentage of diabetic patients having thyroid abnormalities than current study, a high incidence of 46% diabetic patients were showing thyroid dysfunction out of which 26.6% were with hypothyroidism and 19.9% were with [34] and hyperthyroidism was 23% and 3%.[35] Current study results indicated that thyroid hormone imbalance occurs considerably among diabetics, frequently among females, and in the patients having HbA1c >7. When diabetes is accompanied by thyroid dysfunction, these disorders makes it cumbersome to manage and maintain the glucose level of the patient. Thus, the condition becomes more detrimental. Diabetic patients must be regularly evaluated for their thyroid profile on regular intervals. Managing both of these endocrinal disorders will increase the efficiency of treatment and a decrease in the morbidity rate.

Conclusion

Thyroid dysfunction is observed more significantly in females' diabetic patients. Thyroid hormone imbalance occurs considerably among diabetic females that make difficult to maintain the glucose level. Diabetic patients must be regularly evaluated for thyroid profile on regular intervals. Managing both of these endocrinal disorders will increase the efficiency of diabetic treatment and may decrease in the morbidity rate .

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