

The effects of glibenclamide on thyroid function tests in type 2 diabetic patients

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ABSTRACT

Objective: to determine the long-term effect of glibenclamide on thyroid function tests in type 2 diabetic patients.

Materials and methods: A total of 63 diabetic patients, 32 type 2 on glibenclamide and 31 type 1 on insulin, were enrolled in this study. Thirty two, apparently healthy volunteers, were also included in the study as a control group. Blood samples were taken from the patients and controls, then the serum were analysed for measurement of fasting serum glucose (FSG), thyroid hormones (total T3, fT3, total T4, fT4) and TSH.

Results: the result showed that there were no significant differences between thyroid hormones and TSH of the glibenclamide group when compared to the same parameters in the control group, however the fT3 and fT4 of insulin group were significantly lower than that of the control and glibenclamide groups. There were no significant differences between total T3 and total T4 of control, glibenclamide and insulin groups when compared to each others, whereas the TSH of insulin group was significantly higher than that of control and glibenclamide groups.

Conclusion: long term therapy with glibenclamide have no effect on thyroid function tests in type 2 diabetic patients and there was no correlation between glycemic control and thyroid hormones or TSH.

Key words: thyroid hormone, glibenclamide, diabetes mellitus.

الملخص:

الهدف: لبيان تأثير استخدام عقار الجلبيبنكلاميد لفترات طويلة على وظائف الغدة الدرقية لدى مرضى السكري من النوع الثاني.

الطرق المتبعة والأشخاص: اجريت هذه الدراسة في مدينة الموصل. حيث شملت الدراسة 63 مريضا مصابا بداء السكري، 32 مريضا مصابا بداء السكري من النوع الثاني يتعاطون عقار الجلبيبنكلاميد و 31 مريضا مصابا بداء السكري من النوع الاول يتعاطون الانسولين، و 32 شخصا سليما كمجموعة ضبط. اخذت عينات الدم من المرضى ومن مجموعة الضبط وتم تحليل مصل الدم لقياس سكر المصل وفحوصات وظائف الغدة الدرقية وفحص الهرمون المحفز للغدة الدرقية.

النتائج: اظهرت النتائج انه لا يوجد اي فرق معنوي بين فحص هورمونات الغدة الدرقية كافة وفحص الهرمون المحفز للغدة الدرقية لمجموعة عقار الجلبيبنكلاميد عند مقارنتها مع مثيلاتها في مجموعة الضبط بينما يوجد فرق معنوي في فحص هورمونات الغدة الدرقية الحرة لمجموعة الانسولين حيث انها اقل من مجموعة الضبط ومجموعة عقار الجلبيبنكلاميد. لا يوجد اي فرق معنوي بين المجاميع كافة عند مقارنة فحص هورمونات الغدة الدرقية الكلية مع بعضها البعض بينما فحص الهرمون المحفز للغدة الدرقية اعلى في مجموعة الانسولين بشكل معنوي عن المجموعتين الاخرتين.

الاستنتاج: استنتجت الدراسة ان استخدام الجلبيبنكلاميد لفترة طويلة لا يؤثر على فحوصات وظائف الغدة الدرقية لدى مرضى السكري من النوع الثاني ولا يوجد اي علاقة بين مستوى السكر في الدم وفحوصات الغدة الدرقية.

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia resulting from a defect in insulin secretion, insulin action, or both¹. Diabetes mellitus is an endocrine disorder which affect more than 100 million (6% of the population) of people world-wide inspite of enormous facilities available to control its growth². In type 2 diabetes, the β -Cell dysfunction superimposed on insulin resistance leads to hyperglycaemia and subsequently to type 2 diabetes. Typically, at the time of diabetes diagnosis, nearly 50% of β -cell function has been lost and less than 60% of normal insulin sensitivity is present³. Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications⁴. When the strategies of lifestyle modification, diet and exercise of moderate intensity fails to maintain the adequate glycaemic control, oral hypoglycemic agents are introduced as a treatment approach³. Insulin is indicated in diabetes mellitus when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications⁵.

Diabetes and thyroid disease are common in the population, there is a continuous association of thyroid hormones and insulin in glucose metabolism^{6,7}. Many studies revealed that T3 and insulin both stimulate the expression of hexokinases and glycogen synthase which are respectively responsible for uptake and disposal of glucose via formation of glucose-6 phosphate and glucose-1 phosphate⁸. At a molecular level, microarray studies performed on mice liver have demonstrated that most of

the enzymes involved in gluconeogenesis are positively regulated by thyroid hormone⁹. It is known that thyroid hormones can stimulate the expression and activate a number of proteins that are candidates for regulating insulin sensitivity¹⁰. It was reported by Ledda et al.¹¹ that T3 is a powerful inducer of pancreatic acinal cell proliferation in rodents. Ortega et al.¹² demonstrated that T3 concentrations were positively associated with insulin secretions and T3 may play a role in the insulin secretions.

The oral hypoglycemic agents, sulfonylureas, are used by many physicians in the treatment of patients with type 2 diabetes mellitus¹³. Many studies showed a higher incidence of hypothyroidism in diabetics treated with the first generation sulfonylureas than in control groups treated with diet alone or insulin¹⁴. In most patients that are hypofunctional after sulfonylurea therapy, the pituitary is able to compensate for their effect and maintain a euthyroid state by increased synthesis of TSH (compensated hypothyroidism), and goiter is the most striking and best known outcome of excessive TSH secretion. The electrophoretic studies showed that sulfonylureas inhibit the binding of T3 and T4 to thyroid-binding globulin competitively, reduced protein-bound iodine and elevated resin uptake has been used as evidence of their antithyroid property¹⁵.

Trials about the effects of second generation sulfonylureas on the thyroid function is insufficient. Therefore, this study was designed to investigate the effect of glibenclamide on thyroid function tests in type 2 diabetic patients.

Materials and methods

This study was conducted in Mosul-Iraq during the period from 1st of January 2012 to the 1st of August 2012. A total of 63 diabetic patients were enrolled in this study, they were divided into two groups, the first group included 32 type 2 diabetic patients (15 male and 17 female) on glibenclamide therapy; their mean age was 52.51 ± 8.8 years whereas the second group involved 31 type 1 diabetic patients (11 male and 20 female) on insulin therapy; their mean age was 53.41 ± 8.3 years. Another group involved thirty two apparently healthy volunteers (14 male and 18 female), were also included in the study as a control group; their mean age was 50.91 ± 8.2 years.

The study design was case-control study and the patients were excluded if they had a history of hypertension, angina pectoris, myocardial infarction, heart failure, renal or hepatic failure or those taking hypoglycemic agents other than glibenclamide and insulin. Pregnant women and lactating mother were also excluded from the study.

Seven milliliters of venous blood, for laboratory evaluation of biochemical parameters, were obtained from all participants after an overnight fasting (12-hours) by antecubital vein puncture, The blood was allowed to clot at room temperature and after

centrifugation the serum was collected in plane tube and analyzed. Fasting serum glucose was estimated by glucose-oxidase-peroxidase spectrophotometric method, by using a kit supplied by Biocon company (Germany). Thyroid hormones; total triiodothyronine (total T3), free triiodothyronine (fT3), total thyroxine (total T4) and free thyroxine (fT4) and TSH were measured using ELFA (Enzyme Linked Fluorescent Assay) technique (minividas (biomerieux) France), by using kit supplied by Biomerieux company (France).

Statistical analysis

All values expressed as Mean \pm SD and P value of ≤ 0.05 was considered to be statistically significant. Two sample t-test and Pearson's correlation were used to compare the results of various parameters among the studied groups. Statistical analysis was done using Minitab for Windows statistical software, version 14.

Results

Age of the participants, body mass index (BMI), duration of treatment by glibenclamide or insulin and gender are shown in (table 1). There were no significant differences between the studied groups regarding age and BMI.

Table 1: demographic characteristics of the studied groups.

Parameters	Control group (No.=32)	Glibenclamide group (No.=32)	Insulin group (No.=31)
Age (years)	50.91 ± 8.2	52.51 ± 8.8 ^{NS}	53.41 ± 8.3 ^{NS}
BMI (kg/m ²)	27.9 ± 3.5	28.2 ± 3 ^{NS}	29.0 ± 2.53 ^{NS}
Duration of treatment (years)	6.6 ± 3.4	7.5 ± 4.62
Gender (male/Female)	14/18	15/17	11/20

^{NS} Non significant differences as compared to same parameter in the control group (P > 0.5).

Table 2: the FSG, total T3, fT3, total T4, fT4 and TSH for the studied groups.

Parameters	Control group (No.=32)	Glibenclamide group (No.=32)	Insulin group (No.=31)
FSG (mmol/l)	4.9±0.63	11.4±2.82 ^a	10.6±2.4 ^a
fT3(pmol/l)	6.64±2.42	5.36±0.95	4.79±0.42 ^{ab}
fT4(pmol/l)	15.7±2.27	15.35±3.2	12±1.53 ^{ab}
Total T3(nmol/l)	1.69±0.27	1.68±0.36	1.69±0.52
Total T4(nmol/l)	112.2±10.4	103.4±15.4	100.8±13.7
TSH(mIU/l)	1.28±0.65	1.26±1.11	3.84±3.19 ^{ab}

a= significant differences ($P \leq 0.05$) as compared to the same parameters in the control group.

b= significant differences ($P \leq 0.05$) as compared to the same parameters in the glibenclamide group.

Table 3: the Pearson's correlation between FSG and thyroid hormones and TSH.

Mean± SD(No. 63 patients)		FSG (mmol/l)	R	P value
Thyroid function tests				
fT3(pmol/l)	5.1±0.81	10.5±3.25	- 0.177	0.527
fT4(pmol/l)	13.9±3.1	10.5±3.25	- 0.123	0.280
Total T3(nmol/l)	1.7±0.42	10.5±3.25	- 0.128	0.953
Total T4(nmol/l)	102.3±14.5	10.5±3.25	- 0.201	0.590
TSH(mIU/l)	1.92±2.32	10.5±3.25	- 0.113	0.157

There were no significant differences between thyroid hormones and TSH of glibenclamide group when compared to the same parameters in the control group whereas the fT3 and fT4 of insulin group were significantly lower than that of the control and glibenclamide groups. There were no significant differences between total T3 and total T4 of control, glibenclamide and insulin groups when compared to each others, however the TSH of insulin group was significantly higher than that of control and glibenclamide groups (Table 2).

There were non significant mild negative correlation between the FSG and all thyroid hormone parameters and TSH in diabetic patients, as shown in (Table 3).

Discussion

Sulfonylurea drugs are a class of compounds that are developed from sulfonamide drugs by some

modifications, but their effects on iodine metabolism are different from sulfonamides, sulfonylureas decrease the uptake of iodide whereas sulfonamides prevent conversion of iodine to diiodotyrosine and thyroxine, but do not prevent uptake of iodide by the thyroid gland¹⁵. Goitrogenic substances exert effects on the thyroid gland by disrupting one of several steps in the biosynthesis and secretion of thyroid hormones, these include inhibition of the iodine-trapping mechanism, blockage of organic binding of iodine and coupling of iodothyronines to form T4 and T3 and inhibition of thyroid hormone secretion by an effect on the proteolysis of active hormone from the colloid¹⁶. Studies showed that sulfonylureas decrease the thyroid uptake of iodide, Tranquada et al and Skinner et al examined the 24-hour I¹³¹ uptake in rats given sulfonylurea and they showed that the thyroid I¹³¹

uptake was decreased¹⁵.

To exclude the effect of diabetes on thyroid gland, the present study compared thyroid function test of glibenclamide with that of type 1 diabetic patients on insulin therapy. In this study the patient and the control groups were matched regarding age and BMI. This matching has a beneficial effects in that it exclude any effects of differences in age and BMI on the outcome of the study (table 1). The present study found out that there were no significant differences in the thyroid hormones and TSH in the glibenclamide group when compared to same parameters in the control group, these findings were in agreement with other studies^{17,18,19} which were using different types of second generation sulfonylurea but the result obtained in this study were inconsistent with those studies which were using first generation sulfonylurea^{13,14,20}.

The present study found out that the levels of fT3 and fT4 of insulin group were significantly lower than that of glibenclamide and control groups but there were no significant differences between total T3 and total T4 of insulin, glibenclamide and control groups when compared to each others whereas the TSH of insulin group was significantly higher than that of glibenclamide and control groups indicating that insulin group had subclinical hypothyroidism. Many studies^{21,22,23} were in agreement with the present study, reported a reduction in fT3 and fT4 with normal total T3 and total T4 and elevated TSH in both type 1 and type 2 diabetic patients on insulin therapy. Both Rezzonico et al²⁴ and Ayturk et al²⁵ reported that a higher levels of circulating insulin associated with insulin resistance have shown a proliferative effect on thyroid tissue resulting in larger thyroid size with increased formation of nodules.

A study done by Nadez-Real et al²⁶, they suggests peripheral resistance to thyroid hormone action with insulin resistance, the higher the fT4-TSH product, and the lower the insulin sensitivity. In addition to that insulin resistance is responsible about decreased peripheral deiodination of T4. The deiodinases play an important role in the maintenance of circulating and tissue levels of thyroid hormones. The T4 is converted to T3 via type 2 deiodinase in the brain, pituitary and muscle. A decreased activity of type 2 deiodinase could result in decreased intracellular availability of active thyroid hormone in these tissues. The reduction in intracellular T3 would lead to increased serum TSH²⁶.

The present study showed a mild negative correlation between fasting serum glucose levels and parameters of thyroid function test. This may suggests that absence or minimal role of blood sugar concentration in thyroid dysfunction and further studies with glycated hemoglobin may be necessary to find out the role of glycemic status in causing thyroid dysfunction^{18,27}.

Conclusion

Long-term use of glibenclamide has no effect on thyroid function tests, whereas the long-term use of insulin may leads to subclinical hypothyroidism and such patients may require annual screening of their thyroid function in particular in endemic area with goiter and their FSG levels do not predict the risk.

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