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Unraveling the Complex Interplay: Type 1 Diabetes Mellitus, Thyroid Function, and Hepatic Metabolism

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ABSTRACT

This article delves into the intricate relationships between Type 1 Diabetes Mellitus (T1DM), thyroid function, and hepatic metabolism, shedding light on the complex interplay that influences insulin sensitivity, glucose homeostasis, and liver health. The study, conducted at Al-Qadisiyah Teaching Hospital in Iraq from January 2021 to July 2021, involved 60 T1DM patients and 40 healthy controls aged 1 to 16 years.

Results from the investigation revealed significant elevations in thyroid-stimulating hormone (TSH) levels among individuals with diabetes, emphasizing the intricate interplay between T1DM and thyroid function. Moreover, T1DM patients exhibited marked increases in liver enzymes and bilirubin levels, underscoring the potential hepatocellular implications associated with metabolic dysregulation.

Our findings highlight the augmented production of TSH in individuals with diabetes as a potential defensive mechanism to mitigate the consequences of elevated blood glucose. The crucial role of triiodothyronine (T3) in enhancing insulin sensitivity and reducing serum blood glucose levels is emphasized, reinforcing its position as a key player in glucose metabolism.

On hepatic level, the presence of advanced glycation end-products (AGEs) in diabetes amplifies oxidative stress, potentially leading to inflammation and tissue damage in the liver. The study illustrates a model of interaction between hepatic metabolism and T1DM, highlighting the impact of diabetes on liver apoptosis, bilirubin metabolism, and the intricate interplay between high blood sugar levels, AGEs, and red blood cell (RBC) membranes.

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Our findings provide comprehensive insights into the interconnected dynamics of T1DM, thyroid function, and hepatic metabolism, contributing to a deeper understanding of the complex physiological interactions within the context of diabetes mellitus.

INTRODUCTION:

The intricate relationship between glucose metabolism and thyroid hormones, particularly triiodothyronine (T3), assumes a pivotal role in comprehending thyroid function's nuanced impact on insulin sensitivity and glucose homeostasis. Concurrently, its correlation with thyroid-stimulating hormone (TSH) concentrations contributes to evolve understanding of the interplay between thyroid function and glucose regulation.

Shifting our focus to hepatic metabolism, the association between type 1 Diabetes Mellitus (T1DM) and liver oxidative stress takes center stage. Elevated glucose levels stimulate the generation of reactive oxygen species (ROS), potentially leading to inflammation and tissue damage. This phenomenon is further compounded by diabetes-induced advanced glycation end-products (AGEs), intricately intertwining the dynamics of thyroid and liver function.

This article aims to delve into the complex connections between T1DM, thyroid function, and hepatic metabolism. By exploring these interconnections, we seek to unravel the intricacies of the physiological processes that bind these systems together.

METHODS

General Design:

Children with Type 1 Diabetes Mellitus (T1DM) recruited for the study were monitored at Al-Qadisiyah Teaching Hospital, Diabetic Clinic, Al-Qadisiyah Province, Iraq. The control group consisted of apparently healthy subjects. The study was conducted from January 2021 to July 2021.

Inclusion Criteria:

Patients with T1DM aged 1 to 16 years old were included in this study, irrespective of the duration of the disease's evolution. Matched controls with no glucose metabolism abnormalities were also recruited.

Patient Data Collection:

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Data including age, gender, type of treatment, history of renal disease, and history of any other diseases were collected.

Biochemical Assays:

HbA1C was estimated using a special ELISA kit (SUNLONG*). Glucose levels were determined based on an oxidative reaction using the ABBOT kit.

Serum Triiodothyronine (T3), Serum Thyroxine (T4), and Serum TSH were assessed using a special Elisa kit (SUNLONG).

AST was collected through a catalyzed reaction between alpha-ketoglutarate and L-aspartate, producing glutamate and oxaloacetate. In the presence of malate dehydrogenase (MDH), oxaloacetate reacts with NADH, producing malate and NAD. The absorbance is proportional to the AST activity of the sample. Alkaline phosphatase activity was determined using the Spectrum Egypt kit. Alanine aminotransferase concentration was measured using the Spectrum Egypt kit.

RESULTS:

The current study included 100 subjects distributed as follows: 60 T1DM patients and 40 healthy controls. Our results show that age and sex have no marked differences in healthy and DM group in age and sex (Table 1).

The investigation revealed a statistically significant elevation in thyroid-stimulating hormone (TSH) levels among individuals with diabetes mellitus (DM) at a significance level of $p \leq 0.05$. Our analysis demonstrated a notable augmentation in both thyroid hormones, encompassing TSH, with a statistical significance of $p \leq 0.05$, when comparing patients with DM to the control group. These findings underscore the intricate interplay between diabetes mellitus and thyroid function, emphasizing the potential implications of such associations in clinical contexts (Table 2).

Table 1: Age and sex in healthy and DM group

	Control	**Patients**	**P**
N (M/F)	40(20/20)	60(30/30)	-

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Age	10.35±2.60	9.83±2.76	0.56

Within the present investigation, individuals diagnosed with diabetes exhibited markedly elevated concentrations of liver enzymes, including aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT), in comparison to the control cohorts. Moreover, our study discloses a noteworthy escalation in the levels of direct, indirect, and total bilirubin among patients with diabetes mellitus, with statistical significance observed at $p \leq 0.05$ when compared to the healthy control group. These findings illuminate the potential hepatocellular implications associated with diabetes mellitus, underscoring the intricate interrelationship between metabolic dysregulation and hepatic function (Table 3).

Table 2: Thyroid hormones analysis:

	Control	**Patient**	**P**
TSH (mU/ L)	2.57 ± 0.732	3.98 ± 1.23	0.042
T4 (ng/ ml)	9.8 ± 1.38	12.3 ± 2.89	0.023
T3 (pg/ ml)	2630 ± 830.93	4010 ± 660.47	0.017

Table 3: Hepatic function analysis:

	Control	**Patient**	**P**
AST	29.00 ± 3.73	35.00 ± 6.29	0.041
ALP	±216.78 64.71	324.39 ±47.82	0.029
ALT	49.80 ± 7.54	62.51 ± 6.00	0.03
Direct bilirubin (mg/dl)	0.29 ± 0.03	0.41 ± 0.056	0.041
Indirect bilirubin (mg/dl)	0.38 ± 0.15	0.76 ± 0.12	0.033
Total bilirubin (mg/dl)	1.10 ± 0.12	1.85 ± 0.06	0.023

DISCUSSION

Interplay between T1DM and thyroid function

In the realm of endocrinology, recent investigations have spotlighted the augmented production of thyroid-stimulating hormone (TSH) by the anterior pituitary gland in

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individuals with diabetes. This observed increase in TSH levels may be interpreted as a defensive mechanism initiated by the body to mitigate the deleterious consequences of elevated blood glucose. Such a response appears to enhance glucose uptake by various cells, as suggested by Biondi et al.(1) and Schernthaner-Reiter et al.(2).

Furthermore, the intricate orchestration of glucose metabolism has been elucidated, with a central role attributed to thyroid hormones, particularly triiodothyronine (T3). Numerous factors, including T3 levels, metabolic status, and interactions with other hormones, contribute to the nuanced modulation of T3's influence on glucose homeostasis, as delineated by Mullur et al.(3) and Eom et al.(4).

Notably, T3 has emerged as a pivotal player in enhancing insulin sensitivity, thereby facilitating a decline in glucose concentrations. Mechanistically, T3 has been shown to stimulate glucose absorption into cells and promote glucose metabolism, culminating in a reduction in serum blood glucose levels, as reported by Lin and Sun(5).

The intricate conversion of thyroxine, produced by the thyroid gland, into the active T3 by various tissues throughout the body has been underscored(6). T3, the predominant thyroid hormone dictating metabolic processes, exerts a profound impact on protein production, oxygen consumption, and cellular energy utilization. Moreover, studies, such as those by Crunkhorn and Patti, have noted a concurrent elevation in both T3 and thyroxine levels with increasing thyroid-stimulating hormone (TSH) concentrations, particularly in individuals with diabetes. These findings collectively contribute to a comprehensive understanding of the intricate interplay between thyroid function and glucose regulation in the context of diabetes mellitus.

A suggested model of interaction between hepatic metabolism and T1DM

The association between diabetes mellitus and hepatic oxidative stress is a subject of growing scientific interest. Elevated glucose levels over prolonged periods stimulate the generation of reactive oxygen species (ROS) in the liver, potentially culminating in oxidative stress. This phenomenon can inflict damage on biological components such as proteins, lipids, and DNA, contributing to inflammation and tissue damage, as elucidated by studies conducted by Mohamed et al.(7) and Mendes-Braz et al.(8).

Furthermore, diabetes-induced increases in glycation end-products, formed during the interaction of glucose with body proteins, present an additional dimension to the oxidative

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stress landscape. These advanced glycation end-products (AGEs) may amplify oxidative stress by generating ROS, compromising the body's antioxidant defenses. This cascade of events enhances osmotic pressure, potentially leading to tissue inflammation and damage. Notably, the accumulation of AGEs in the liver has been implicated in impairing liver health and impeding its normal physiological function, as reported by Leung et al.(9) and Rungratanawanich et al.(10).

The impact of diabetes on liver apoptosis is also noteworthy, with evidence suggesting accelerated apoptotic processes. High glucose concentrations associated with diabetes can activate cellular pathways, including the activation of caspase-3, a key component of the apoptotic pathway, as described by Ingaramo et al.(11) and Meisse et al.(12). While diabetes itself does not directly induce organized cell death in the liver, poorly controlled diabetes may trigger various biological pathways supporting apoptosis in liver cells, potentially contributing to elevated liver enzyme levels, in line with the findings of Montane et al. and Giri et al.(13).

In the context of bilirubin metabolism, diabetes mellitus appears to impact the liver's ability to effectively process bilirubin. This impairment results in an accumulation of bilirubin in the blood, reflected in increased serum bilirubin levels, according to the insights presented by Vítek(14). This observation diverges from the findings of Wang et al.(15), who reported increased bilirubin concentrations in newly onset diabetes that subsequently decreased with the progression of diabetic duration.

Moreover, the intricate interplay between high blood sugar levels, advanced glycation end-products, and red blood cell (RBC) membranes is highlighted. High sugar concentrations can induce the formation of AGEs, contributing to RBC membrane destruction and hemolysis, which, in turn, elevates bilirubin levels in the blood, as discussed by Chappey et al.(16) and Pernow et al.(17).

The present study aligns with existing research indicating that hemolysis in diabetes can lead to an increase in bilirubin levels. Excessive breakdown of RBCs may overwhelm the liver's capacity to process bilirubin efficiently, resulting in elevated serum bilirubin levels, consistent with the findings of Mireles et al.(18).

Lastly, diabetes mellitus may exert an impact on the kidneys' ability to eliminate bilirubin, especially in cases of severe or prolonged diabetes. High sugar concentrations and increased

pressure in diabetes can damage kidney blood vessels, leading to impaired kidney function, known as diabetic nephropathy. This condition may hinder the effective removal of bilirubin by the kidneys, contributing to elevated blood levels of bilirubin, as discussed by Koren et al.(19) and Thomas et al.(20).

CONCLUSION:

The orchestrated modulation of glucose metabolism, particularly the role of triiodothyronine (T3), emerges as a key player in enhancing insulin sensitivity and reducing serum blood glucose levels. Notably, our research aligns with existing literature, indicating that diabetes-induced hemolysis may contribute to elevated bilirubin levels, potentially overwhelming the liver's processing capacity. This study provides comprehensive insights into the interconnected dynamics of T1DM, thyroid function, and hepatic metabolism. The findings contribute to a deeper understanding of the complex physiological interactions, shedding light on potential mechanisms within the context of diabetes mellitus.

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