
Assessment of serum fucose, protein-bound fucose, and lipid-associated fucose in primary hypothyroidism

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ABSTRACT

Background and objective: Primary hypothyroidism is a prevalent endocrine disorder marked by reduced production of thyroid hormones, which disrupts metabolic homeostasis and may influence glycosylation. Fucosylation, a type of glycosylation, is required for immune system function and cell communication. Serum levels of Total Fucose (TF), Protein-Bound Fucose (PBF), and Lipid-Associated Fucose (LAF) have been observed to change in various diseases, but their role in primary hypothyroidism is unclear. This study evaluated serum TF, PBF, and LAF levels in patients with primary hypothyroidism to determine whether they could support diagnosis.

Methods: This case-control study included individuals diagnosed with primary hypothyroidism and matched healthy controls. Serum levels of TF, PBF, and LAF were measured spectrophotometrically. Thyroid function tests (TSH, FT3, and FT4) were also evaluated. Statistical comparisons, Pearson correlation analyses, and Receiver Operating Characteristic (ROC) curve analyses were performed to assess diagnostic utility.

Results: Significantly elevated levels of TF (33.86 ± 2.82 vs. 17.90 ± 1.61 mg/dL), PBF (12.97 ± 1.47 vs. 8.50 ± 1.10 mg/dL), and LAF (4.11 ± 0.13 vs. 2.69 ± 0.37 mg/dL) were observed in the hypothyroid group compared with controls ($p < 0.0001$ for all). TF, PBF, and LAF showed strong positive correlations with TSH and strong negative correlations with FT3 and FT4. ROC curve analysis revealed excellent diagnostic performance for all three parameters.

Conclusion: Serum TF, PBF, and LAF are significantly elevated in primary hypothyroidism patients ($n=50$) compared with healthy controls ($n=50$) and strongly correlate with thyroid hormone levels. These markers demonstrate excellent diagnostic accuracy and may serve as diagnostic markers in primary hypothyroidism.

Keywords: Primary hypothyroidism, Total fucose, Protein-bound fucose, Lipid-associated fucose, Glycoconjugate

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INTRODUCTION

Primary hypothyroidism occurs when the thyroid gland does not produce enough hormones (1, 2). It is a common disease that leads to metabolic disruption and harmful effects on cells throughout several organs. Carbohydrate, protein, and lipid metabolism all depend on thyroid hormones, so their deficiency can cause dyslipidemia, excess body weight, and abnormal glycoprotein production (3). Hypothyroidism goes beyond its usual effects on metabolism and also influences glycosylation, which is necessary to maintain the structure and function of various biomolecules (4).

Glycoconjugates — for instance, glycoproteins and glycolipids — are built by combining carbohydrates with proteins or lipids using covalent bonds. They serve important functions in how cells communicate, how the immune system works, how signals are processed, and how the extracellular matrix is structured (5). Among the monosaccharides important in glycosylation, L-fucose, a terminal deoxyhexose sugar, appears to be crucial in embryogenesis, inflammation, immune modulation, and cancer progression (6).

Adding fucose residues via fucosylation is handled by fucosyltransferases. Fucosylation changes have been noted in malignancies, autoimmune syndromes, and some metabolic disorders (7). Total fucose (TF), protein-bound fucose (PBF), and lipid-associated fucose (LAF) have been shown to change in many disease conditions (8). Major changes in glycoprotein metabolism occur in Hashimoto's thyroiditis and similar autoimmune thyroid diseases (9). Studies have noted that core fucose on immunoglobulin G (IgG) is lower and sialylation is higher in serum glycoproteins of affected patients, suggesting a link between glycosylation and the thyroid's immune processes (10). Moreover, thyroid hormones appear to play a role in determining

how much fucosyltransferases are expressed in the liver, meaning they directly affect fucose metabolism (11).

Despite the established link between thyroid function and glycosylation, there is insufficient data on serum fucose and its related parameters in primary hypothyroidism. Prior work has found that people with hypothyroidism have increased fucose levels, pointing to problems with glycosylation resulting from hormone imbalance (5), but little is known about fucose profiling in this domain. Since fucose appears to be involved in thyroid disease and metabolism, investigating serum levels of fucose and its related parameters in primary hypothyroidism might bring new understanding of the fucosylation process. This study examines these glycoconjugate parameters in people with primary hypothyroidism to evaluate their potential use as biomarkers in clinical practice.

METHODS

Study Design

This is a case-control study designed to evaluate serum fucose and its related parameters in 50 male patients newly diagnosed with primary hypothyroidism and 50 healthy male controls.

Study Setting

The study was conducted at the Clinical Biochemistry Department, College of Health Sciences, Hawler Medical University, in collaboration with the local Endocrinology Center in Erbil, Iraq.

Inclusion Criteria

Participants included male adults aged 18–50 years who were newly diagnosed with primary hypothyroidism. All participants were not yet receiving thyroid hormone replacement therapy

and were free from any acute illness or infection at the time of enrollment.

Exclusion Criteria

Individuals with a history of other thyroid disorders, such as hyperthyroidism, thyroid cancer, or non-autoimmune thyroiditis, were excluded. Participants were also excluded if they had systemic diseases, including diabetes, or cardiovascular, renal, or hepatic conditions. Those with autoimmune diseases unrelated to thyroiditis, or those using medications known to interfere with thyroid function or fucose metabolism (such as glucocorticoids or immunosuppressants), were not eligible.

Ethical Considerations

The study proposal was officially approved by the Scientific Committee of Hawler Medical University (approval number 11F, dated 26 September 2024) and the Hawler Directorate of Health's Ethical Committee.

Blood Sample Collection

Ten milliliters of venous blood were collected from patients with primary hypothyroidism (n=50) and healthy controls (n=50) using standard venipuncture into yellow-top (serum separator) tubes. After clotting, samples were centrifuged at 3000 rpm for 15 minutes. This study was conducted at Galiawa Diabetes and Endocrinology Teaching Center in Erbil, over a period of three months. Thyroid function tests (TSH, FT3, and FT4) were measured directly; for fucose-related parameters, serum was aliquoted into two sterile Eppendorf tubes and stored at -80°C until analysis.

Methodology

1. Serum TSH was measured using the LIAISON® TSH kit (REF: 311211) on the LIAISON® XL analyzer (12).
2. Serum FT3 was measured using the LIAISON® FT3 kit (REF: 315311) on the LIAISON® XL analyzer (13).
3. Serum FT4 was measured using the LIAISON® FT4 kit (REF: 311611) on the LIAISON® XL analyzer (14).
4. Serum Total Fucose (TF) was estimated using the Dische and Shettles method, based on the reaction of concentrated sulfuric acid with fucose-containing components in serum. The reaction mixture, combined with cysteine hydrochloride, produces a color complex measured spectrophotometrically at 396 nm and 430 nm (15).
5. Serum Protein-Bound Fucose (PBF) was determined using the Dische and Shettles method. Serum proteins were first precipitated, then redissolved in NaOH. In the presence of concentrated acid and cysteine hydrochloride, fucose reacted to form a colored complex, measured spectrophotometrically at 396 nm and 430 nm (15).
6. Serum Lipid-Associated Fucose (LAF) was determined using the Katopodis method (16).

Statistical Analysis

Data were presented as mean $\pm$ standard deviation (SD). Statistical analysis was performed using GraphPad Prism (version 9). Group comparisons were conducted using Student's t-test, and Pearson's correlation coefficient (r) was used to evaluate relationships between variables. Receiver Operating Characteristic (ROC) curve analysis was

applied to assess the diagnostic performance of selected markers.

RESULTS

Table 1 lists the results of thyroid function tests and fucose-related markers in both the primary hypothyroidism group and the control group. Patients with primary hypothyroidism had a much higher mean $\pm$ SD TSH level (15.36 ± 2.989) than the control group (2.282 ± 0.3398), a highly significant difference ($p < 0.0001$). By contrast, mean serum free thyroxine (FT4) was much lower in the primary hypothyroidism group (0.5574 ± 0.1439) than in controls (1.228 ± 0.1485), also highly significant ($p < 0.0001$). Likewise, primary hypothyroidism

patients had significantly lower serum free triiodothyronine (FT3) (1.706 ± 0.2298) compared with controls (3.036 ± 0.3257 , $p < 0.0001$).

Fucose-related tests found that the primary hypothyroidism group had a much higher serum Total Fucose (TF) level (33.86 ± 2.823) than controls (17.90 ± 1.613 , $p < 0.0001$). Serum Protein-Bound Fucose (PBF) in hypothyroid patients (12.97 ± 1.471) was considerably higher than in healthy individuals (8.503 ± 1.104), also highly significant ($p < 0.0001$). Similarly, the primary hypothyroidism group had a higher mean $\pm$ SD serum Lipid-Associated Fucose (LAF) than controls ($p < 0.0001$).

Table 1. Mean $\pm$ SD of serum TSH, FT4, FT3, TF, PBF, and LAF in primary hypothyroidism and control groups

Parameter	Hypothyroidism	Control	p
TSH (mIU/L)	15.36 ± 2.989	2.282 ± 0.3398	<0.0001
FT4 (ng/dL)	0.5574 ± 0.1439	1.228 ± 0.1485	<0.0001
FT3 (pg/mL)	1.706 ± 0.2298	3.036 ± 0.3257	<0.0001
TF (mg/dL)	33.86 ± 2.823	17.90 ± 1.613	<0.0001
PBF (mg/dL)	12.97 ± 1.471	8.503 ± 1.104	<0.0001
LAF (mg/dL)	4.107 ± 0.1349	2.69 ± 0.3734	<0.0001

Table 2 shows the correlation between fucose and thyroid function parameters. There was a strong positive correlation between TF and TSH ($r = 0.919$, $p < 0.001$), and TF was strongly negatively correlated with FT4 ($r = -0.892$, $p < 0.001$) and FT3 ($r = -0.903$, $p < 0.001$). Similarly, PBF was strongly positively correlated with TSH ($r = 0.830$, $p < 0.001$) and strongly negatively correlated with FT4 ($r = -0.802$, $p < 0.001$) and FT3 ($r = -0.771$, $p < 0.001$). LAF showed a strong positive correlation with TSH ($r = 0.887$, $p < 0.001$) and strong negative correlations with FT4 ($r = -0.864$, $p < 0.001$) and FT3 ($r = -0.875$, $p < 0.001$). These results indicate

that serum fucose parameters are closely linked to changes in thyroid hormone levels.

ROC curve analysis of the fucose markers likewise showed strong performance in distinguishing primary hypothyroidism from healthy controls. TF was highly effective, with a cutoff of 13.58 achieving both sensitivity and specificity of 1.000. PBF showed similarly excellent results, with a cutoff of 5.23 giving 100% accuracy for both sensitivity and specificity. LAF also performed well, with a cutoff of 1.01 giving both sensitivity and specificity a perfect score of 100%.

Table 2. Correlation between fucose parameters and thyroid function tests

Parameter	vs TSH	vs FT4	vs FT3
TF	$r=0.919$, $p<0.001$	$r=-0.892$, $p < 0.001$	$r=-0.903$, $p < 0.001$
PBF	$r=0.830$, $p < 0.001$	$r=-0.802$, $p < 0.001$	$r=-0.771$, $p < 0.001$
LAF	$r=0.887$, $p < 0.001$	$r=-0.864$, $p < 0.001$	$r=-0.875$, $p < 0.001$

DISCUSSION

This study showed increased levels of serum total fucose (TF), protein-bound fucose (PBF), and lipid-associated fucose (LAF) in patients with primary hypothyroidism compared with healthy individuals. Fucose metabolism appears to be significantly altered when thyroid hormone decreases, and these glycoconjugate markers may point to key changes that occur in hypothyroidism.

According to the study results, serum total fucose was elevated in hypothyroidism, consistent with findings of raised serum fucose in other diseases such as diabetes, cancer, and liver disease (6, 17, 18). Many glycoproteins and glycolipids contain fucose, which supports cell signaling,

affects the immune system, and is involved in inflammatory processes (6). The increase in fucosylated biomolecules in hypothyroidism may result from increased production or decreased breakdown of these biomolecules, since thyroid hormones play a role in the function of fucosyltransferases in the liver (19).

Protein-bound fucose (PBF) was also found to be higher than in controls, which further supports the notion that glycoprotein metabolism is altered in people with hypothyroidism (20). This could occur due to increased production or decreased clearance of fucosylated serum proteins, as seen during an immune or inflammatory (acute-phase) reaction (21). Studies have shown that autoimmune

thyroid disorders such as Hashimoto's thyroiditis usually lead to alterations in immunoglobulin structure, including reduced core fucosylation (9, 22). The increase in serum PBF found in this study implies that other types of serum glycoproteins are similarly affected by the hormonal imbalances involved.

It is also noteworthy that LAF (lipid-associated fucose) increased substantially, demonstrating possible changes in glycolipid metabolism due to primary hypothyroidism. Because thyroid hormones regulate lipid movement and membrane composition, changes in lipid levels in hypothyroid patients may affect how fucosylated glycolipids are incorporated and displayed (23).

A strong positive relationship was found between serum fucose and serum TSH, and a strong negative relationship with serum FT3 and FT4. These continuous relationships indicate that as thyroid hormone deficiency worsens, fucose metabolism changes become more pronounced, adding weight to the view that thyroid hormones help regulate the fucosyltransferases responsible for clearing glycoproteins and glycolipids in the liver (5, 22).

ROC analysis suggests that TF, PBF, and LAF have strong diagnostic value, with each reaching 100% sensitivity and specificity at a given threshold, so fucose biomarkers could support the early detection of primary hypothyroidism — consistent with the broader principle that novel serum biomarkers, such as visfatin in subclinical hypothyroidism, can add diagnostic value alongside standard thyroid testing (24, 25). While thyroid-stimulating hormone (TSH) remains the cornerstone of diagnosis, glycan-based markers may offer additional detail about disease severity, its effects on the body, or may help identify subclinical cases early (26).

The ROC curve results demonstrate a strong link between fucose parameters and thyroid dysfunction, suggesting that they could serve as reliable biomarkers to help diagnose primary hypothyroidism.

Despite the strength of these findings, several limitations must be acknowledged. Autoimmune and non-autoimmune types of hypothyroidism were not differentiated in this study, which could affect glycosylation differently.

CONCLUSION

The present study revealed significantly increased levels of TF, PBF, and LAF in primary hypothyroidism patients compared with controls. These parameters correlated strongly with thyroid hormones and showed excellent diagnostic accuracy, indicating their potential use as reliable biomarkers for primary hypothyroidism.

COMPETING INTEREST

The authors declare that they have no competing interests.

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