Study on the Effect of Follicle Simulating Hormone on Lipid Metabolism in Postmenopausal T2DM and Potential Mechanisms

Yining Gong\textsuperscript{1,a,#}, Qian Wang\textsuperscript{1,b,#}, Shulong Shi\textsuperscript{2,c}, Yongping Wang\textsuperscript{1,d}, Jian Li\textsuperscript{3,e}, Dandan Yin\textsuperscript{1,f}, Dehuan Kong\textsuperscript{4,g,*}, Yaping Liu\textsuperscript{2,h,*}

\textsuperscript{1}Jining Medical University, Jining, 272000, China
\textsuperscript{2}Department of Endocrinology, Jining No. 1 People’s Hospital, Jining, Shandong, 272000, China
\textsuperscript{3}Department of Osteoarticular Surgery, Jining No. 1 People’s Hospital, Jining, Shandong, 272000, China
\textsuperscript{4}Department of Diabetes and Metabolic Diseases, The Affiliated Taian City Central Hospital of Qingdao University, Taian, Shandong, 271000, China
\textsuperscript{a}E-gongyining0917@163.com, \textsuperscript{b}wangq3505@163.com, \textsuperscript{c}529306267@qq.com, \textsuperscript{d}wyp17865703892@163.com, \textsuperscript{e}38858622@qq.com, \textsuperscript{f}1750594695@qq.com, \textsuperscript{g}kdhsmile@163.com, \textsuperscript{h}liuyaping409972352@163.com

\textsuperscript{#}These authors contribute equally.
\textsuperscript{*}Corresponding author

Keywords: Follicle-Stimulating Hormone, Dyslipidemia, T2DM (Diabetes Mellitus Type 2), Bioinformatics Analysis, Molecular Mechanism

Abstract: The purpose of our study was to analyze the relationship between serum FSH levels and TC, TG, LDL-C, HDL-C in postmenopausal T2DM patients and further explore the potential molecular mechanisms of FSH affecting lipid metabolism in postmenopausal T2DM via data mining online databases for associations between FSH and Dyslipidemia. Methods used in this paper. The first was a retrospective study of 279 postmenopausal patients with natural gestational type 2 diabetes mellitus (T2DM) admitted to the Department of Endocrinology of the First People’s Hospital of Jining City from October 2020 to October 2022. Secondly, target genes for postmenopausal T2DM and lipid metabolism complications were retrieved from GeneCard, OMIM and GEO databases. Compound-target, protein-protein interaction (PPI) and compound-target-pathway networks were created using Cytoscape software. GO and KEGG pathway analyses were also performed to identify possible enrichment of genes with specific biological themes. The results obtained in this study are the age group of 50 to 60 years was demonstrated to have the most significant FSH levels in postmenopausal T2DM patients. Compared with the low FSH group, the TG level in the high FSH group significantly increased (P<0.05). The GeneCards database selected 2,113 pathogenic targets for T2DM, 878 targets for the postmenopausal period, and 335 pathogenic targets for dyslipidemia. Among them, INS, ALB, IL-6, TNF, PPARG, LEP, ADIPOQ, APOE, CRP, and APOB ranked in the top 10 nodes in terms of degree value and the AGE-RAGE signaling pathway dominated the KEGG signaling pathway. Further investigation in postmenopausal T2DM patients aged 50 to 60 years demonstrated a favorable connection between serum TG, FSH, IL-6. We conclude that, first, The FSH level reaches its peak secretion period in postmenopausal T2DM patients aged 50-60 years. Second, Serum TG levels in postmenopausal T2DM patients aged 50-60 are positively
correlated with FSH. Third, FSH may exacerbate lipid metabolism disorders in postmenopausal T2DM patients aged 50-60 by activating the inflammatory cytokine IL-6. Fourth, AGE-RAGE, AMPK, and TNF signaling pathways may lead to abnormal blood lipids in postmenopausal T2DM.

1. Introduction

Diabetes Mellitus (DM) is a complex endocrine and metabolic disorder, chiefly characterized by hyperglycemia. The primary etiology of the disorder can be ascribed to inadequate insulin secretion, insulin resistance, or a blend of both, which leads to glucose metabolism dysregulation. In recent years, there has been a marked surge in the prevalence of DM. As per 2021 estimates, the global prevalence of DM in the age group of 20-79 reached 10.9%, with Type 2 Diabetes Mellitus (T2DM) accounting for over 90% of the total worldwide DM cases [1]. The escalation of T2DM and its complications have significantly inflated the global mortality and morbidity rates. Traditionally, T2DM complications are partitioned into macrovascular complications, such as Cardiovascular Disease (CVD), and microvascular complications involving renal, retinal, and neurological disorders. CVD is primarily responsible for the increased incidence and mortality rate [2].

Serum follicle-stimulating hormone (FSH) is one of the essential gonadotropins involved in mammalian reproduction and development. It is synthesized by gonadotropic cells (a type of basophilic cell) in the anterior lobe of the pituitary gland (adenohypophysis) and then secreted into the blood [3]. Not only does FSH regulate gonadal function, but it also influences body fat, thermogenesis, serum cholesterol, osteoporosis, and the incidence of cardiovascular diseases, even affecting the aging process [4, 5]. Studies have shown that with the rise in FSH levels after menopause, the incidence of dyslipidemia in women decreases [6]. Some distinct studies suggest a significant positive linear relationship between postmenopausal FSH and TC, LDL-C, identifying FSH as an independent risk factor for dyslipidemia in postmenopausal women [7, 8].

This study, through bioinformatics analysis, found that the occurrence of dyslipidemia in postmenopausal T2DM may be related to multiple aspects such as insulin resistance, abnormal energy metabolism, increased oxidative stress response, and inflammatory response. This provides new insights for the lipid-lowering treatment and research direction for postmenopausal T2DM patients.

2. Methodology

2.1 Research target

This study conducted a retrospective collection of data on postmenopausal T2DM patients who were treated in the Department of Endocrinology at the Jining No 1 People's Hospital from October 2020 to October 2022. Approval for the study was granted by the Ethics Committee of the Jining No 1 People's Hospital, and informed consent was obtained from each participant.

2.2 Serum Indicator Tests

Fasting venous blood samples were collected early in the morning (after fasting for more than 8 hours). Levels of TG, TC, LDL-C, HDL-C, FBG, HbA1c, TSH, PTH, and Vitamin D were determined using a fully automated biochemical analyzer. Each marker was meticulously sampled, submitted for analysis, and tested in accordance with prescribed procedures and operational standards.
2.3 Acquisition of postmenopausal T2DM and lipid metabolism disorders targets

By searching the keywords “type 2 diabetes”, “dyslipidemia”, and “postmenopause”, the known related targets were retrieved from two public database, including GeneCard (http://www.genecards.org/), and Online Mendelian Inheritance in Man (OMIM, http://www.omim.org/) database. Considering the integrity of research data, we performed differential gene expression analysis with some postmenopausal T2DM and lipid metabolism disorders sample from Gene Expression Omnibus database (GEO, https://www.ncbi.nlm.nih.gov/geo/).

2.4 Network construction and analysis

In order to reveal the common pathogenic mechanism of postmenopausal T2DM and dyslipidemia, we established the protein-protein interaction (PPI) pathway. We established the degree value of each node in the key gene protein-protein interaction (PPI) network; the higher the degree value, the more essential the gene. The core gene (Hub gene) is identified by employing the top 30 results with a relatively high degree value. Subsequently, the genes were arranged by degree value and presented in a histogram format.

Cross-sectional study of postmenopausal T2DM and dyslipidemia targets for common potential targets of postmenopausal T2DM and dyslipidemia. Then, these predictive targets were imported into the STRING (https://string-db.org/) database, with a confidence score set to 0.4 and the species restricted to “Homo sapiens”. The data of PPI were saved as “TSV” format, and then submitted to Cytoscape software for constructing PPI network graph. In PPI network, hub genes, namely key therapeutic targets, were screened out by calculating Degree Centrality (DC), Betweenness Centrality (BC), Closeness Centrality (CC), Eigenvector Centrality (EC), and Local average connectivity-based method (LAC) with the Cytoscape plugin CytoNCA.

2.5 Enrichment analysis

The Gene Ontology (GO) analysis can provide a standardized description and annotation for genes and gene products. Through GO analysis, users can obtain a comprehensive understanding from several aspects, including biological process (BP), cellular component (CC), and molecular function (MF). The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a commonly used resource for the systematic analysis of gene functions and related high-level genome functional information. In order to investigate the biological pathways of pathogenic genes in PPI network, three installed R packages (“DOSE”, “clusterProfiler”, “pathview”) were applied to analyze GO and KEGG pathway enrichment and adjusted p-value < 0.05 was considered statistically significant. The top 20 results from the GO and KEGG pathway analyses were depicted in bubble plots and bar charts, addressing the primary molecular mechanisms and signaling pathways of dyslipidemia observed in postmenopausal T2DM.

2.6 Data Analysis

Measurements were expressed as mean ± standard error of the mean (SEM), with statistical significance being accentuated for differences exhibiting a p-value less than 0.05. Applications like SPSS or GraphPad Prism 9.3.1 was utilized to conduct statistical assessments and produce illustrative visualizations. Preliminary verification of data normality was performed prior to any analysis. Data from more than two groups were analyzed using one-way ANOVA or multiple comparisons; data from two groups were analyzed using independent-sample t-tests (two independent-sample t-tests) or rank-sum tests. Furthermore, regression analyses were executed on corresponding evaluations impacting TG.
3. Results

3.1 Basic clinical characteristics and biochemical indicators of the study population

A total of 226 postmenopausal patients with T2DM met the criteria of this study. The age range was between the ages of 50 and 84, with an average age of 62.40 ± 7.36 years. The general conditions and characteristics of the clinical data are presented in Table 1.

Table 1: General Characteristics for Clinical Data

<table>
<thead>
<tr>
<th>Project/Age</th>
<th>50-60 years (n=105)</th>
<th>61-70 years (n=87)</th>
<th>&gt;70 years (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Disease(years)</td>
<td>8.64±1.30</td>
<td>8.45±1.63</td>
<td>9.01±1.72</td>
</tr>
<tr>
<td>BMI(Kg/M²)</td>
<td>23.66±0.33</td>
<td>24.79±0.34</td>
<td>24.32±0.62</td>
</tr>
<tr>
<td>E2(pmol/L)</td>
<td>32.44±2.07</td>
<td>31.42±2.35</td>
<td>30.71±3.21</td>
</tr>
<tr>
<td>FSH(mIU/ml)</td>
<td>62.23±2.57</td>
<td>55.51±1.85</td>
<td>50.88±3.50</td>
</tr>
<tr>
<td>TC(mmol/L)</td>
<td>5.07±0.10</td>
<td>4.80±0.13</td>
<td>4.41±0.20</td>
</tr>
<tr>
<td>TG(mmol/L)</td>
<td>1.53±0.06</td>
<td>1.53±0.08</td>
<td>1.47±0.21</td>
</tr>
<tr>
<td>HDL-C(mmol/L)</td>
<td>1.32±0.04</td>
<td>1.23±0.03</td>
<td>1.27±0.06</td>
</tr>
<tr>
<td>LDL-C(mmol/L)</td>
<td>3.24±0.09</td>
<td>3.07±0.11</td>
<td>2.69±0.15</td>
</tr>
<tr>
<td>FBG(mmol/L)</td>
<td>9.54±0.42</td>
<td>9.28±0.40</td>
<td>9.00±0.80</td>
</tr>
<tr>
<td>HbA1c(%)</td>
<td>9.74±0.25</td>
<td>8.90±0.25</td>
<td>9.72±0.34</td>
</tr>
<tr>
<td>TSH(μIU/ml)</td>
<td>2.14±0.13</td>
<td>2.41±0.16</td>
<td>2.05±0.23</td>
</tr>
<tr>
<td>PTH(pg/ml)</td>
<td>34.59±1.64</td>
<td>38.38±1.60</td>
<td>33.68±2.50</td>
</tr>
<tr>
<td>Vitamin D(ng/ml)</td>
<td>19.22±0.71</td>
<td>17.54±0.70</td>
<td>17.66±0.86</td>
</tr>
</tbody>
</table>

3.2 Univariate analysis of biochemical indicators in postmenopausal T2DM patients of different age groups

Figure 1 (A-N) delineates the outcomes of a one-way ANOVA and subsequent multiple comparisons of clinical parameters across three age cohorts of postmenopausal T2DM patients. The findings underscored that serum FSH levels were considerably elevated in the 50–60 years age compared to those over 70 years age (P <0.05), indicating that FSH secretion peaks during the 50–60 years age range and subsequently experiences a progressive decline with ageing. In comparison to the cohort exceeding 70 years, the concentrations of TC and LDL-C exhibited a significant elevation in the 50–60 years age group (P<0.001). Pertaining to variables such as disease duration, hypertension (HT), weight (WT), body mass index (BMI), estradiol (E2), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), and vitamin D, no statistically noteworthy divergence was detected among the three groups(P>0.05).
Note: Three groups were investigated: The the 50–60 years age group (n=105), 61-70 years age group (n=87), along with > 70 years age group (n=34); HT, WT, BMI, HbA1c, FBG, E2, FSH, TG, TC, HDL-C, LDL-C, TSH, PTH, and Vitamin D were all detected. A statistically significant difference is indicated by the icons *P<0.05, **P<0.001, and P<0.05.

Figure 1: Comparison of postmenopausal T2DM patients of various ages' biochemical signatures

3.3 Analysis of lipid metabolism indexes between groups with different FSH levels

To explore the potential association between FSH and lipid alterations in postmenopausal T2DM patients, the study focused on the 50–60-year-old cohort manifesting elevated levels of FSH and lipids. Participants were bifurcated into two distinct groups based on their median FSH value (56.72mIU/ml): The low-FSH group (n=53 participants) and the high-FSH group (n=52 participants), and a statistically significant divergence was observed in FSH levels between these two clusters (P<0.0001). As shown in Figure 2 (A-G), the study's conclusions indicated no statistically significant changes between the two groups for E2, BMI, TC, HDL-C, LDL-C, FBG, and HbA1c, while TG level was markedly elevated in the high FSH group compared to its low FSH counterpart (P< 0.001). This study failed to establish correlation between FSH and TC, LDL-C, or HDL-C.
Note: \( n = 52 \) in the high level FSH group and \( n = 53 \) in the low level FSH group; FSH (A), BMI (B), E2 (C), LDL-C (D), TG (E), TC (F), and HDL-C (G). Statistically significant differences are represented by symbols such as \(* * * P < 0.001, **** P < 0.0001, \) and \( P < 0.05 \).

Figure 2: E2 and Cholesterol Comparison in Postmenopausal T2DM Patients with Different FSH levels

3.4 Prediction and Intersection of Targets Related to Postmenopausal T2DM and Dyslipidemia

Upon inputting the terms "type 2 diabetes mellitus", "postmenopause", and "dyslipidemia" into the GeneCards database, a compilation of 2113 T2DM-associated targets, 878 postmenopause-associated targets, and 335 dyslipidemia-associated targets were procured. Following an intricate cross-reference of these identified targets using Cytoscape software to generate Venn diagrams, a set of 97 presumptive pathogenic targets, shared across postmenopausal T2DM and dyslipidemia, was discerned as illustrated in Figure 3.

Figure 3: Venn Diagram of Potential Pathogenic Targets for Lipid Abnormalities in Postmenopausal T2DM
3.5 KEGG Signaling Pathway Enrichment Analysis and GO Function

Figure 4: GO Functional Enrichment Analysis Bubble Chart (Top 20)

Figure 5: KEGG signaling pathway enrichment map (top 20)

The outcomes of the GO functional annotation predominantly pertain to receptor ligand activity,
lipoprotein particle binding, steroid binding, protein-lipid complex binding, hormone activity, nuclear receptor activity, among others. As depicted in Figure 4, receptor ligand activity is notably significant. The horizontal coordinates represent the gene ratio, while the vertical coordinates correspond to GO-enriched terms. The color symbolizes the degree of enrichment, and the bubbles illustrate that how many genes are enriched to each entry. The degree of enrichment is greater, the more red the color, the smaller the P-value.

The pathogenesis of lipid and atherosclerosis (LAS) emerged as the most significantly enriched domain in the KEGG signaling pathway enrichment analysis, as illustrated in Figure 5. The horizontal coordinates denote the number of co-expressed genes, while the vertical coordinates exhibit the name of the KEGG pathway where these co-expressed genes are enriched. The P-value is indicated by the color intensity, with a deeper red hue signifying a smaller P-value and greater enrichment level. Other KEGG-enriched pathways elucidated in Figure 5 include AGE-RAGE signaling pathway in diabetic complications, AMPK signaling pathway, insulin resistance, TNF signaling pathway, fluid shear stress, and atherosclerosis. Dyslipidemia in postmenopausal T2DM has been associated with sundry causes encompassing insulin resistance, altered energy metabolism, heightened oxidative stress, and inflammatory response.

3.6 Co-acting Target PPI Network and Hub Gene Screening Construction

A PPI network with 97 common targets was generated, demonstrated, and evaluated in this assessment. As depicted in Figure 6, 93 nodes are contained. The top 30 genes were chosen as Hub genes, and they were subsequently presented in a bar graph by degree value, with a higher degree value emphasizing a gene's value, which was depicted in Figure 7. INS, ALB, IL-6, TNF, PPAR, LEP, ADIPOQ, APOE, CRP, and APOB exhibited elevated degree values. The PPI network illustration gives insights into how the hypothesized targets might interact with each other, potentially contributing to dyslipidemia in postmenopausal T2DM.

Figure 6: PPI Network
3.7 Linear Regression Analysis between FSH and TG, FSH and IL-6, IL-6 and TG in Postmenopausal T2DM Patients

Postmenopausal T2DM complicated with dyslipidemia implicates an inflammatory response, and according to bioinformatics analysis, the key gene (a significant target) in this process is the inflammatory cytokine IL-6. In this study, participants aged 50 to 60 years demonstrated a statistically significant correlation between serum FSH and IL-6 levels, as depicted in Fig. 8A. By leveraging the median TG value, postmenopausal T2DM patients aged 50 to 60 years were classified into two groups: the low level group with TG ≤ 1.345 (mmol/L), and the high level group with TG > 1.345 (mmol/L). According to the results, the IL-6 level in the high-TG group was significantly elevated compared to that in the low-TG group (P <0.05), which is depicted in Fig. 8B. As illustrated in Tables 2, 3, and 4, further linear regression analyses examining the relationships between FSH and TG, FSH and IL-6, and IL-6 and TG in postmenopausal T2DM patients revealed that serum TG was positively correlated with both FSH and IL-6 in these patients (B=0.009, P=0.022; B=0.138, P=0.038), and IL-6 exhibited a positive correlation with FSH (B=0.034, P <0.001).
Figure 8: Comparison of IL-6 Levels in 50-60 Year Old Postmenopausal T2DM Patients with Different FSH and TG Levels (*P<0.05)

Table 2: FSH and TG Linear Regression Investigation in Postmenopausal T2DM Patients

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>P</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>0.009</td>
<td>0.022</td>
<td>1.001~1.017</td>
</tr>
</tbody>
</table>

Note: TG is the strain variable

Table 3: Linear Regression Analysis between FSH & IL-6 in postmenopausal T2DM Patients

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>P</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>0.034</td>
<td>&lt;0.001</td>
<td>1.017~1.053</td>
</tr>
</tbody>
</table>

Note: IL-6 is the strain variable

Table 4: Linear regression analysis between IL-6 and TG in postmenopausal T2DM patients

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>P</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.138</td>
<td>0.038</td>
<td>1.008~1.308</td>
</tr>
</tbody>
</table>

Note: TG is the strain variable

4. Discussions

The pituitary gland synthesizes and secretes FSH, a glycoprotein hormone consisting of two subunits, α and β. For the hormone to maintain its biological activity, both subunits are indispensable. The β subunit exhibits hormone specificity and engages in particular biological actions through its interaction with the Follicle Stimulating Hormone Receptor (FSHR)\(^9\). Recent findings indicate that FSHR—categorized as a G protein-coupled receptor (GPCR)—is expressed not only in gonads but also in osteoclasts and chicken adipose tissue. FSH plays integral roles beyond bone mass regulation; it also influences fat accumulation and distribution in humans\(^{15, 10, 11}\). Notably, there is a pronounced correlation between serum FSH levels and conditions such as postmenopausal osteoporosis and obesity.

In this investigation, although there was a trend toward lower E2 levels as postmenopausal age increased, there was no statistically significant difference. The serum FSH levels in postmenopausal...
T2DM patients reached their zenith between the aged 50-60 years, thereafter continually decreasing with advancing age, which aligns with previous studies[12]. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly elevated in T2DM patients aged 50-60 years compared to those over 70 years. This coincided with the peak secretion of blood FSH, suggesting a potential role of FSH in lipid metabolism abnormalities in these patients.

In this study, we subdivided the 50-60 years old age group based on FSH levels into high and low FSH subgroups. TG prevalence was significantly higher in the high FSH subgroup, thus supporting the hypothesis that elevated FSH may contribute to lipid metabolism abnormalities in postmenopausal T2DM patients. A prospective cohort study illustrated a significant positive linear relationship between postmenopausal FSH, TC, and LDL-C, particularly in younger postmenopausal women (53-62 years old). Higher FSH levels have been linked with an increased likelihood of high TC and LDL-C levels, even after adjusting for estrogen and conventional confounders [3, 7, 8]. These were consistent with our findings.

According to studies on epidemiology, there is a significant correlation between postmenopausal serum FSH and TC, TG, and LDL-C [6, 7, 13]. FSH impacts the lipid metabolism of postmenopausal T2DM patients. The balance of cholesterol is largely sustained by the liver, where FSH can regulate metabolic processes such as lipid synthesis and transport. Functional FSH receptors (FSHR) were identified in human liver tissue; deficiency in these receptors in postmenopausal women prevents hepatic cholesterol accumulation and lowers serum cholesterol levels [8]. Ovariectomized mice with elevated serum FSH and cholesterol levels exhibited reduced hepatic LDL receptor expression as per Song et al. This suggests that FSH, by binding to FSHR in a dose- and time-dependent manner, can elevate LDL-C levels, possibly by inhibiting LDL receptor production in the liver and reducing LDL-C degradation [14]. The rate-limiting enzyme for the generation of cholesterol is HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase), and simple FSH levels elevation promotes HMGCR expression and activity, which in turn stimulates cholesterol the manufacturing process. The main mechanism of action is FSH binding to the Gi2α/β-arrestin2/ FoxO1/Akt/SREBP-2 signaling pathway, which is mediated by FSHR. A diet high in cholesterol or FSH can increase cholesterol, nevertheless an anti-FSH antibody can stop this from arising [8]. The starting point of the reaction for the synthesis of TGs and the oxidation of fatty acids in vivo is catalyzed by ACSL (Long-chain acyl-CoA synthetase), which converts fatty acids with 12 to 20 carbon chains into fatty acid coenzyme A. However, higher concentrations of the ACSL isozyme ACSL3 correspond to lower levels of TG and free lipids in the serum and liver [15], the mechanism of which is not clear. Some research asserted that FSH has a negative connection with TG, which is contradictory to our findings. [6, 13]. In order to determine if FSH lowers TG levels via the TNF-α/ACSL3 pathway, experimental data is required to establish that TNF-α boosts ACSL3 protein expression [14].

T2DM needs to have chronic low-grade inflammation of the pancreatic islets. Insulin resistance and adipose tissue dysfunction are common consequences of T2DM. Pro-inflammatory cytokines like TNF-α and IL-6 are created when adipose tissue fails to function, contributing to systemic insulin resistance and low-grade inflammation. On the other hand, insulin resistance intensifies the low-grade inflammatory state in addition to developing hyperglycemia. [16, 17].

In this study, postmenopausal T2DM patients between the ages of 50 and 60 showed a favorable correlation between serum FSH levels and TG. TNF-α and IL-6 were among the primary pathogenic genes in postmenopausal T2DM dyslipidemia, suggesting that they were involved in or influenced T2DM lipid metabolism. Bioinformatics analysis additionally indicated that postmenopausal T2DM dyslipidemia was significantly linked to inflammatory response and insulin resistance. According to a linear regression investigation, TG was positively connected with IL-6 and FSH, and IL-6 was positively correlated with FSH, indicating that serum TG levels in postmenopausal T2DM patients were influenced by both FSH and IL-6. According to some investigations, FSH could
contribute to lipid metabolism difficulties among T2DM patients by stimulating inflammatory molecules like IL-6. According to Chen Lingxia et al., TG was favorably associated with serum IL-6, TNF-α, and CRP in T2DM patients. T2DM patients had greater serum levels of TG and IL-6 compared to non-DM patients, although CRP and TNF-α did not vary statistically from non-DM patients. Inflammatory response and TG are thought to be closely interconnected, and IL-6 may be a more sensitive indication than increases in TNF-α and CRP [18]. Additionally, it has been demonstrated that BMI and IL-6 levels in DM patients were directly associated to insulin resistance, and that female DM patients were more susceptible to insulin resistance as inflammatory mediator levels rise [19]. Insulin resistance and IL-6 have a considerable direct link, and according to research conducted by Pouresmaeil et al [20].

Multifunctional cytokine IL-6 has complicated effects on inflammation, glucolipid metabolism, and bone metabolism. It is produced by immune cells, adipocytes, beta-cells in the pancreas, and other cell types [21, 22]. IL-6 affects the control of glucolipid metabolic balance in a number of ways that are beneficial and detrimental. Skeletal muscle cells in contraction release IL-6, which improves insulin sensitivity and boosts fat oxidation to reduce body fat. By stimulating the AMP/AMPK pathway, acute IL-6 therapy improves glucose uptake and fat oxidation in skeletal muscle. On the other hand, IL-6 produced by adipose tissue causes insulin resistance in the liver. According to earlier research, acute IL-6 administration greatly decreases the activity of the IRS-1 and IRS-2-associated PI3K (phosphatidylinositol 3 kinase), which results in insulin resistance in the skeletal muscle and liver [23, 24]. McNeill discovered that, independently of changed peripheral IL-6 signaling, central IL-6 deletion animals with a high-fat diet, they showed enhanced hepatic steatosis and raised hepatic TG, indicating that central IL-6 signaling mechanisms may be essential for preserving lipid and glucose homeostasis [25]. Anti-IL-6 immune system antibodies motivate glucose uptake and lipid oxidation by up-regulating the expression of AMPK and PPAR in skeletal muscle to reduce insulin resistance, obesity, and hepatic steatosis degeneration. IL-6-induced insulin resistance in skeletal muscle is the main contributory factor of these conditions [26].

5. Conclusion

In summation, there is a discernible positive correlation between serum TG levels and FSH in postmenopausal T2DM patients aged 50-60 years. Furthermore, it has been observed that FSH levels reach their zenith secretory phase in this particular demographic. Through the stimulation of the proinflammatory cytokine IL-6, FSH could potentially exacerbate dyslipidemia in postmenopausal T2DM patients aged 50-60 years. Several molecular signaling pathways, including AGE-RAGE, AMPK, and TNF, may be implicated in the dyslipidemia associated with postmenopausal T2DM.

The association between FSH and lipid profiles in postmenopausal T2DM elucidates new avenues for therapeutic strategies aimed at lipid reduction. The detection of inflammatory biomarkers is necessary for the systematic diagnosis of dyslipidemia complicated by T2DM, and the control of inflammatory mediator levels aids in the management of T2DM and its complications. Furthermore, Low-peak inflammation promotes the progression of T2DM and lipid metabolism disorders.

Data accessibility

The authors will supply the relevant data in response to reasonable requests.

Author contributions

Yining Gong, Qian Wang: Writing - Original Draft, Validation, Formal analysis, Visualization. Shulong Shi: Methodology, Formal analysis
Acknowledgement

This research was financially supported by Jining City key research and development plan project (2021YXNS005)

References


