Mini Review

Journal of Diabetes & Metabolic Syndrome

The Relationship between Non-Alcoholic Fatty Liver Disease and Thyrotropin Levels in Patients with Type 2 Diabetes Mellitus: A Mini Review

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Abstract

Abundant studies have showed that both hypothyroidism and subclinical hypothyroidism are associated with Non- Alcoholic Fatty Liver Disease (NAFLD). Besides, NAFLD and Type 2 Diabetes Mellitus (T2DM) regularly coexist, which act synergistically and lead to many adverse outcomes. However, the relationship between NAFLD and thyrotropin levels (TSH) in T2DM patients remains unknown. This mini review sought to examine the evidence about association between TSH levels and NAFLD. We found that TSH level may be an independent risk factor for NAFLD in patients with T2DM. In doing so, this review may provide novel insight and highlight that further studies are needed to explore the mechanisms and targeted treatment.

Keywords: Non-alcoholic fatty liver disease; Thyrotropin; Type 2 diabetes mellitus

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Received Date: September 20, 2021

Accepted Date: October 08, 2021

Published Date: October 14, 2021

Citation: Fu Y, Tang X, Tan Y, Zhu Y (2021) The Relationship between Non-Alcoholic Fatty Liver Disease and Thyrotropin Levels in Patients with Type 2 Diabetes Mellitus: A mini review. J Diab Meta Syndro 4: 014.

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is emerging as a public health burden worldwide with a histological spectrum ranging from steatosis to Non-Alcoholic Steato Hepatitis (NASH) and cirrhosis [1,2]. It has been recognized as one of the most prominent causes of chronic liver diseases, steeply rising a worldwide prevalence to 25% in 2019 [1,3,4]. A significant body of evidence holds the view that NAFLD is a multisystem disease [5] and increases the risk of developing cardiometabolic diseases, including Type 2 Diabetes (T2DM) [6]. Pathologically, NAFLD is closely related to the characteristic of Insulin Resistance (IR) and metabolic syndrome [7]. The global prevalence of NAFLD among patients with T2DM is 55.5% [8]. These two conditions could act synergistically and lead to many adverse outcomes, including liver-related mortality and all-cause mortality [5,9]. Thus, identifying the risk factors for NAFLD in advance is essential to reduce the liver-mortality of patients with T2DM.

It is well-known that thyroid hormones regulate various metabolic processes, including carbohydrates, lipids, and proteins. Thyroid hormone is involved in hepatic lipid metabolism and hepatic IR [10]. Previous studies have revealed that both hypothyroidism and subclinical hypothyroidism are associated with NAFLD [11-13]. Our previous study has demonstrated that high-normal Serum thyrotropin (TSH) levels were significantly associated with the presence of NAFLD in patients with T2DM with euthyroid function [14]. Thyroid function and T2DM are both closely associated with increased risks of NAFLD. To date, few review exist regarding the association between NAFLD and thyroid hormone in T2DM patients. Therefore, this mini-review summarizes literatures exploring the association of thyrotropin level and NAFLD in clinical evidences, as well as comprehensively elaborate the role and related mechanisms of thyrotropin in T2DM patients with NAFLD, aiming to provide the mechanism-based therapeutic strategies for clinicians to manage NAFLD in patients with T2DM.

Clinical Evidence

The association of thyrotropin level and NALFD

Thyroid hormones regulate various metabolic processes and exert important roles in hepatic lipid metabolism. There is considerable evidence to support the negative role of increased TSH level in the development of NAFLD. Chung, et al. [12] revealed that TSH levels was related to NAFLD in a dose-dependent manner among patients with subclinical hypothyroidism. Similarly, the other study [15] demonstrated that the spectrum of hypothyroidism including subclinical hypothyroidism and low-normal thyroid function is independently associated with NAFLD and advanced fibrosis in a dose-dependent manner. Notably, high TSH levels have been reported to be associated with the severity of hepatic steatosis [16]. In addition, in euthyroid subjects, several studies have demonstrated that high TSH levels are associated with the risk of NAFLD [15,17-20]. Janovsky et al. [19] found that higher TSH values were associated with higher prevalence of NAFLD (OR=1.22; p<0.01). In addition, Tahare et al. [20] detected that TSH levels was an independent risk factor of NAFLD after multivariate adjustment (OR=1.12; p=0.033). Furthermore, in euthyroid patients with overweight or obese children [21] or adolescents [22], chronic hepatitis B (CHB) [23], elevated TSH concentration is a significant risk for hepatic steatosis. However, these association was not observed in Gökmen FY, et al. study [24]. Considering some systematic review and meta-analysis were performed to explore these inconsistence [13,25,26], we preferred to support that TSH levels may increase the risk of NAFLD, regardless of thyroid function status.

The association of thyrotropin level and T2DM

It is well known for decades that thyroid hormones are important mediators of glucose homeostasis [27,28]. Thyroid hormones could regulate circulating insulin and control intestinal absorption of glucose as well as hepatic gluconeogenesis [29]. Several studies have shown that a low-normal thyroid hormone level is associated with high Fasting Plasma Glucose (FPG) levels and a high glycosylated hemoglobin (HbA1c) level [30]. Furthermore, higher-normal serum TSH levels were associated with the incidence of T2DM [31]. A longitudinal study has demonstrated that TSH levels was associated with the values of glycosylated hemoglobin (HbA1c) and Fasting Plasma Glucose (FPG) and that there was an increased risk of NAFLD with increasing levels of HbA1c independent of obesity [32]. In addition, in euthyroid subjects, a high-normal TSH level was significantly related to insulin resistance and increased glycemic variability and may contribute to glycemic disorders [30,33,34], revealing an increased risk of prevalence of diabetes. Concordantly, a 7-year prospectively study [35] elucidated that baseline concentration of TSH was associated with T2DM in a large cohort of euthyroid subjects and gradually increased TSH was an independent risk of developing diabetes regardless of sex and thyroid autoimmunity. A higher but in normal range serum TSH level was closely related to central obesity and hyperlipidemia in patients with T2DM, which plays a crucial role in the pathogenesis of NAFLD [36]. Combine, a high-normal TSH level may be supposed as a significant additional risk factor for the NAFLD in T2DM patients.

The association of thyrotropin level and patients with T2DM and NALFD

Considering the clinical evidence indicating TSH level be associated the risk of NALFD and exacerbated metabolic disorders in patients with T2DM, it is likely that TSH plays an important role in the incidence of NAFLD in patients with T2DM. However, limited data exist exploring the association between TSH levels and NAFLD in patients with T2DM. In a cross-sectional study included 2289 adults with T2DM [14], our team revealed that a high-normal TSH level was an independent risk factor for NAFLD in patients with T2DM ($p<0.05$), which was consistent with another study with small sample [37], showing that NAFLD in euthyroid T2DM patients may be associated with thyroid hormone resistance-like manifestation. From a diverse aspect, a case-control study [38] suggested that elevated Thyroid Per Oxidase Anti-Body (TPOAb) titer is closely related to NAFLD. Eveline et al. [39] demonstrated that low-dose levothyroxine reduces intrahepatic lipid content in T2DM patients. Consequently, TSH levels may be considered as a significant risk factor of NAFLD in T2DM and more studies are needed to confirm these association.

Potential Mechanisms

Considering NAFLD is common amongst individuals with T2DM, there is emerging evidence revealing a detrimental outcome for people with co-existent diabetes and NAFLD. The relationship between these two conditions could be explained by insulin resistance and compensatory hyperinsulinemia, which leads to abnormal lipid metabolism and hepatic triglyceride accumulation in NAFLD [40]. One of the sources of the accumulation of triacylglycerol (TAG) within the liver comes from De Novo Lipogenesis (DNL) [41], which is increased in a state of hyperinsulinemia, such as insulin resistance [42]. Although the mechanism for the association between TSH levels and an increase risk of NAFLD in patients with T2DM remains elusive, some possible mechanisms are available to explain the relationship. Increased TSH levels were associated with increased triglyceride concentrations, visceral obesity, and reduced insulin sensitivity, which may promote the occurrence of NAFLD [31]. In addition, alteration in serum levels of cytokines and adipokines will influence liver inflammation and increase lipogenesis [43]. The level of TSH could affect the value of adipokines, contributing to the development of NAFLD [44,45].

TSH combined with Thyroid Stimulating Hormone Receptor (TSHR) is an important form to regulate thyroid function. TSHR also expresses in extra-thyroid tissues and cells, such as liver, kidney and brain [46]. Therefore, the study showed that TSH combined with TSHR on hepatocytes could increase the concentration of triglycerides in hepatocytes and promote hepatic steatosis [47]. Furthermore, it has been long known that Sterol Regulatory Element Binding Proteins (SREBPs) are the general name of three major nuclear transcription factors of regulating lipid metabolism. Among them, SREBP-1c, mainly expressed in liver and adipocytes, is directly involved in the regulation of expression of enzymes related to fatty acid and triglyceride synthesis [48]. In addition, Peroxisome Proliferator Activated Receptors (PPARs) are ligand activated nuclear transcription factors with three subtypes. PPARa plays an important role in liver fat synthesis, energy stability as well as glucose and lipid metabolism [49]. TSH regulates triglyceride anabolism mainly through cAMP/PKA/PPARa signal pathway and affects the phosphorylation state of SREBP-1c to involve in the regulation of triglyceride anabolism [50].

The above mechanisms could contribute to the development of hepatic steatosis. Of note, NAFLD accounts for one of the worldwide clinical and financial burden and its incidence is increasing steeply, it is essential to make every potential attempt to understand its various possible etiologies better.

TSH-based therapeutic strategies

There are several possible TSH-based pharmacological strategies for NALFD in patients with T2DM in clinical practice. Based on above evidence indicating the elevated TSH level may promote or aggravate NAFLD, TSH-targeted strategies may be emerged for the treatment of NAFLD.

Thyroid hormone accelerates energy metabolism by upregulation of AMP-Activated Protein Kinase (AMPK) [51], which is an energy sensor, enhancing insulin sensitivity [52]. Given its crucial role, the AMPK pathway has been extensively studied as a potential therapeutic target. Metformin is the first line therapeutic agent in the management of T2DM patients, exerting significant roles in lowering body fat and improve hepatic insulin sensitivity by acting on the AMPK pathway [53]. Metformin may be served as one of TSH-targeted strategies. A prospective study found that metformin was associated with low TSH levels among patients with treated hypothyroidism [54]. In consistent, Al-Alusi, et al. [55] found that metformin suppressed TSH levels and Cappelli, et al. [56] showed a vital decrease in TSH levels in euthyroid patients after metformin therapy.

Thyroid Hormone (TH) has favorable metabolic effects [10], including the ability of reducing low-density lipoprotein cholesterol dramatically [57,58]. Apart from dyslipidemia, there is mounting evidence showing that the supply of thyroid hormone is beneficial for various rodent models of NAFLD [59-61]. Through TH-derived therapies, TH and TH analogs decreased hepato-steatosis. Additional-

ly, Low-dose levothyroxine (LT4) could decrease Intrahepatic Lipid Content (IHLC) in euthyroid male patients with T2DM. This indicated that TH or TH analogs may be another possible treatment of NAFLD in patients with T2DM [39].

Discussion

This review revealed that a high-normal TSH level may be an independent risk factor for NAFLD in T2DM patients. NAFLD and T2DM regularly coexist, increasing the risks for liver-related mortality and all-cause mortality. Some studies have showed that thyroid hormone disorder contributes the development of NAFLD and T2DM [39,62,63]. In addition, in euthyroid subjects, high TSH levels are associated with the risk of NAFLD [16,18]. Our previous study [14] provided a strong rationale in evaluating the risk of NAFLD in T2DM. However, it was a cross-sectional study having limited power to reflect the causal effect of TSH levels on NAFLD in T2DM patients. In addition, few data exist exploring the relationship between serum thyroid hormone levels in the normal range and NAFLD in patients with T2DM. In doing so, this review highlighted that no randomized controlled trial has yet prospectively measured the association between high-normal TSH levels and the risk of NAFLD. Owing to NAFLD is common among individuals with T2DM, there is also an urgent need for prospective trials to identify this kind of relationship and relevant mechanisms. Given limited treatment strategy, other studies are needed to investigate the role of TSH in the development of NAFLD in patients with T2DM and the potential targeted therapy. All in all, this review identified critical science gaps that need to be filled if TSH level is an independent risk in the development of NAFLD, so that thyroid hormone levels should be considered in evaluating the risk of NAFLD in T2DM patients and providing targeted treatment to maximize therapeutic benefit.

References

1. Rinella ME (2015) Nonalcoholic Fatty Liver Disease. JAMA 313: 2263-2273.
2. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, et al. (2018) The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 67: 328-357.
3. Younossi Z, Tacke F, Arrese M, Sharma BC , Mostafa I, et al. (2019) Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology 69: 2672-2682.
4. Byrne CD, Patel J, Scorletti E, Targher G (2018) Tests for diagnosing and monitoring non-alcoholic fatty liver disease in adults. BMJ 362: k2734.
5. Byrne CD, Targher G (2015) NAFLD: A multisystem disease. J Hepatol 62: S47-S64.
6. Mantovani A, Byrne CD, Bonora E, Targher G (2018) Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. Diabetes care 41: 372-382.
7. Hogden A, Greenfield D, Nugus P, Kiernan MC (2012) Engaging in patient decision-making in multidisciplinary care for amyotrophic lateral sclerosis: The views of health professionals. Patient Prefer Adherence 6: 691-701.
8. Younossi ZM, Golabi P, Avila DL, Paik JM, Srishord M, et al. (2019) The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 71: 793-801.
9. Bril F, Cusi K (2016) Nonalcoholic Fatty Liver Disease. Endocrin Metab Clin 45: 765-781.
10. Sinha RA, Singh BK, Yen PM (2018) Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol 14: 259-269.
11. Mantovani A, Nascimbeni F, Lonardo A, Zoppini G, Bonora E, et al. (2018) Association Between Primary Hypothyroidism and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. Thyroid 28: 1270-1284.
12. Chung GE, Kim D, Kim W, Yim JY, Park MJ, et al. (2012) Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatol 57: 150-156.
13. He W, An X, Li L, Shao X, Li Q, et al. (2017) Relationship between Hypothyroidism and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. Front Endocrinol 8: 335.
14. Tan Y, Tang X, Mu P, Yang Y, Li M, et al. (2021) High-Normal Serum Thyrotropin Levels Increased the Risk of Non-Alcoholic Fatty Liver Disease in Euthyroid Subjects with Type 2 Diabetes. Diabetes, metabolic syndrome and obesity 14: 2841-2849.
15. Kim D, Kim W, Joo SK, Bae JM, Kim JH, et al. (2018) Subclinical Hypothyroidism and Low-Normal Thyroid Function Are Associated With Nonalcoholic Steatohepatitis and Fibrosis. Clin Gastroenterol Hepatol 16: 123-131.
16. Carulli L, Ballestri S, Lonardo A, Lami F, Violi E, et al. (2013) Is nonalcoholic steatohepatitis associated with a high-though-normal thyroid stimulating hormone level and lower cholesterol levels? Intern Emerg Med 8: 297-305.
17. Berg EHVD, Wind LJNVT, Amini M, Faber KN, Blokzijl H, et al. (2017) Higher free triiodothyronine is associated with non-alcoholic fatty liver disease in euthyroid subjects: The Lifelines Cohort Study. Metabolism 67: 62-71.
18. Liu Y, Wang W, Yu X, Qi X (2018) Thyroid Function and Risk of Non-Alcoholic Fatty Liver Disease in Euthyroid Subjects. Ann Hepatol 17: 779-788.
19. Janovsky CCPS, Cesena FH, Valente VAT, Conceição RDDO, Santos RD, et al. (2018) Association between Thyroid-Stimulating Hormone Levels and Non-Alcoholic Fatty Liver Disease Is Not Independent from Metabolic Syndrome Criteria. European Thyroid Journal 7: 302-307.
20. Tahara K, Akahane T, Namisaki T, Moriya K, Kawaratani H, et al. (2020) Thyroid-stimulating hormone is an independent risk factor of non-alcoholic fatty liver disease. JGH Open 4: 400-404.
21. Pacifico L, Bonci E, Ferraro F, Andreoli G, Bascetta S, et al. (2013) Hepatic Steatosis and Thyroid Function Tests in Overweight and Obese Children. Int J Endocrinol 2013: 1-8.
22. Kaltenbach TEM, Graeter T, Oeztuerk S, Holzner D, Kratzer W, et al. (2017) Thyroid dysfunction and hepatic steatosis in overweight children and adolescents. Pediatr Obes 12: 67-74.
23. Ding W, Wang M, Wang G, Shen F, Qin J, et al. (2015) Thyroid function is associated with non-alcoholic fatty liver disease in chronic hepatitis B-infected subjects. J Gastroenterol Hepatol 30: 1753-1758.
24. Gökmen FY, Ahbab S, Ataoğlu HE, Türker BC, Çetin F, et al. (2016) FT3/FT4 ratio predicts non-alcoholic fatty liver disease independent of metabolic parameters in patients with euthyroidism and hypothyroidism. Clinics 71: 221-225.
25. Eshraghian A, Jahromi AH (2014) Non-alcoholic fatty liver disease and thyroid dysfunction: A systematic review. World J Gastroentero 20: 8102-8109.
26. Gor R, Siddiqui NA, Wijeratne FR, Nair As, Illango J, et al. (2021) Unraveling the Role of Hypothyroidism in Non-alcoholic Fatty Liver Disease Pathogenesis: Correlations, Conflicts, and the Current Stand. Cureus 13: e14858.
27. Dimitriadis GD, Raptis SA (2001) Thyroid hormone excess and glucose intolerance. Exp Clin Endocr Diab 2: S225-S239.

28. Boelen A (2009) Thyroid hormones and glucose metabolism: The story begins before birth. Exp Physiol 94: 1050-1051.

29. Brenta G, Caballero AS, Te Nunes M (2019) Case Finding for Hypothyroidism Should Include Type 2 Diabetes and Metabolic Syndrome Patients: A Latin American Thyroid Society (LATS) Position Statement. Endocr Pract 25: 101-105.

30. Garduño-Garcia JDJ, Alvirde-Garcia U, López-Carrasco G, Mendoza MEP, Mehta R, et al. (2010) TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol 163: 273-278.

31. Gu Y, Li H, Bao X, Zhang Q, Liu L, et al. (2017) The Relationship Between Thyroid Function and the Prevalence of Type 2 Diabetes Mellitus in Euthyroid Subjects. J Clin Endocrinol Metab 102: 434-442.

32. Jun JE, Jin S, Jee JH, Bae JC, Hur Ky, et al. (2017) TSH increment and the risk of incident type 2 diabetes mellitus in euthyroid subjects. Encocrine 55: 944-953.

33. Iwen KA, Schröder E, Brabant G (2013) Thyroid Hormones and the Metabolic Syndrome. European Thyroid Journal 2: 83-92.

34. Su J, Zhao L, Zhang X, Cai HL, Huang HY, et al. (2018) High-normal serum thyrotropin levels and increased glycemic variability in type 2 diabetic patients. Endocrine 61: 68-75.

35. Jun JE, Jee JH, Bae JC, Jin SM, Hur KY, et al. (2017) Association Between Changes in Thyroid Hormones and Incident Type 2 Diabetes: A Seven-Year Longitudinal Study. Thyroid 27: 29-38.

36. Giandalia A, Russo GT, Romeo EL, Alibrandi A, Villari P, et al. (2014) Influence of high-normal serum TSH levels on major cardiovascular risk factors and Visceral Adiposity Index in euthyroid type 2 diabetic subjects. Endocrine 47: 152-160.

37. Huang B, Yang S, Ye S (2020) Association between Thyroid Function and Nonalcoholic Fatty Liver Disease in Euthyroid Type 2 Diabetes Patients. J Diabetes Res 2020: 1-7.

38. Wang C, Niu Q, Lv H, Li Q, Ma Y, et al. (2020) Elevated TPOAb is a Strong Predictor of Autoimmune Development in Patients of Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Case-Control Study 13: 4369-4378.

39. Bruinstroop E, Dalan R, Cao Y, Bee YM, Chandran K, et al. (2018) Low-Dose Levothyroxine Reduces Intrahepatic Lipid Content in Patients With Type 2 Diabetes Mellitus and NAFLD. The Journal of Clinical Endocrinology & Metabolism103: 2698-2706.

40. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW (2016) Non-alcoholic fatty liver disease and diabetes. Metabolism 65: 1096-1108.

41. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, et al. (2005) Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 115: 1343-1351.

42. Schwarz JM, Linfoot P, Dare D, Aghajanian K (2003) Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets. AM J Clin Nutr 77: 43-50.

43. Musso G, Gambino R, Durazzo M, Biroli G, Carello M, et al. (2005) Adipokines in NASH: Postprandial lipid metabolism as a link between adiponectin and liver disease. Hepatology 42: 1175-1183.

44. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, et al. (2004) Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology 40: 46-54.

45. Gong N, Gao C, Chen X, Wang Y, Tian L (2018) Adipokine expression and endothelial function in subclinical hypothyroidism rats. Endocr Connect 7: 295-304.

46. Williams GR (2011) Extrathyroidal expression of TSH receptor. Annales Endocrinologie 72: 68-73.

47. Tian L, Song Y, Xing M, Zhang W, Ning G, et al. (2010) A novel role for thyroid-stimulating hormone: Up-regulation of hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. Hepatology 52: 1401-1409.

48. Horton JD, Goldstein JL, Brown MS (2002) SREBPs: Activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 109: 1125-1131.

49. Kota B, Huang T, Roufogalis B (2005) An overview on biological mechanisms of PPARs. Pharmacol Res 51: 85-94.

50. Porstmann T, Santos CR, Griffiths B, Cully M, Wu M, et al. (2008) SREBP Activity Is Regulated by mTORC1 and Contributes to Akt-Dependent Cell Growth. Cell Metab 8: 224-236.

51. Garcia D, Hellberg K, Chaix A, Wallace M, Herzig S, et al. (2019) Genetic Liver-Specific AMPK Activation Protects against Diet-Induced Obesity and NAFLD. Cell Rep 26: 192-208.

52. Jung TW, Kim HC, Abd EA, Jeong JH (2018) Maresin 1 attenuates NAFLD by suppression of endoplasmic reticulum stress via AMPK-SERCA2b pathway. J Biol Chem 293: 3981-3988.

53. He X, Wu D, Hu C, Xu T, Liu Y, et al. (2019) Role of Metformin in the Treatment of Patients with Thyroid Nodules and Insulin Resistance: A Systematic Review and Meta-Analysis. Thyroid 29: 359-367.

54. Fournier JP, Yin H, Yu OH, Azoulay L (2014) Metformin and low levels of thyroid-stimulating hormone in patients with type 2 diabetes mellitus. CMAJ 186: 1138-1145.

55. Al-Alusi MA, Du L, Li N, Yeh MW, He X, et al. (2015) Metformin Does Not Suppress Serum Thyrotropin by Increasing Levothyroxine Absorption. Thyroid 25: 1080-1084.

56. Cappelli C, Rotondi M, Pirola I, Agosti B, Formenti A, et al. (2012) Thyreotropin levels in diabetic patients on metformin treatment. Eur J Endocrinol 67: 261-265.

57. Sjouke B, Langslet G, Ceska R, Nicholls SJ, Nissen SE, et al. (2014) Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): A randomised, double-blind, placebo-controlled phase 3 study. The Lancet Diabetes & Endocrinology 2: 455-463.

58. Elbers LPB, Kastelein JJP, Sjouke B (2016) Thyroid Hormone Mimetics: The Past, Current Status and Future Challenges. Curr Atheroscler Rep 8: 14.

59. Cable EE, Finn PD, Stebbins JW, Hou J, Ito BR, et al. (2009) Reduction of hepatic steatosis in rats and mice after treatment with a liver-targeted thyroid hormone receptor agonist. Hepatology 49: 407-417.

60. Vatner DF, Weismann D, Beddow SA, Kumashiro N, Erion DM, et al. (2013) Thyroid hormone receptor-β agonists prevent hepatic steatosis in fat-fed rats but impair insulin sensitivity via discrete pathways. Am J Physiol-Endoc M 305: E89-E100.

61. Finan B, Clemmensen C, Zhu Z, Stemmer K, Gauthier K, et al. (2016) Chemical Hybridization of Glucagon and Thyroid Hormone Optimizes Therapeutic Impact for Metabolic Disease. Cell 167: 843-857.

62. Guo Z, Li M, Han B, Qi X (2018) Association of non-alcoholic fatty liver disease with thyroid function: A systematic review and meta-analysis. Dig Liver Dis 50: 1153-1162.

63. Oda T, Taneichi H, Takahashi K, Togashi H, Hangai M, et al. (2015) Positive association of free triiodothyronine with pancreatic beta-cell function in people with prediabetes. Diabet Med 32: 213-219.

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