Original Article

The comparison of GDM therapeutic methods between positive and negative anti TPO patients

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Abstract

Background: Gestational diabetes mellitus (GDM) is defined as glucose intolerance due to insulin resistance during pregnancy. This metabolic disorder includes 8.3% of pregnancies worldwide. Thyroid gland autoantibodies can induce insulin resistance probably because of inflammatory cytokines production. However, a distinct mechanism of this phenomenon has not well understood. Objectives: Regarding the high prevalence of GDM which concerns the mother and fetus health, this study aimed to compare the therapeutic methods frequency in GDM patients with or without anti-thyroperoxidase (TPO) autoantibodies. Methods: One hundred and two GDM patients aged between 20-30 years, with (n=52) or without (n=50) anti-TPO antibodies were enrolled in this experimental study. Overt hypothyroidism or hyperthyroidism, creatinine>1.4 mg/dl, Congestive Heart Failure, liver diseases, and diabetes history were considered as exclusion criteria. Insulin administration was performed in patients with fasting blood glucose (FBS)>105 mg/dl. Other patients regarding the blood glucose level were treated by metformin or diet. All patients were followed up for one week. Results: Patients were divided into anti-TPO (+) and anti-TPO (-) groups with the average age of 25.52±3.35 and 26.28±3.53, respectively. Significant differences were observed in FBS, 1hour BS and 2 hour BS levels between groups (p=0.003, p=0.041 and p=0.007 for FBS, 1 hour BS and 2 hour BS, respectively). Based on therapeutic methods, significant differences were observed in insulin (p=0.026) and diet (p=0.03) therapy. Conclusion: Our data showed that the presence of anti-TPO antibody is correlated with GDM severity, indicating the importance of thyroid gland function on feto-maternal health status.

Keywords: Gestational diabetes mellitus, Insulin therapy, Anti-thyroperoxidase antibody, Diet therapy, Metformin therapy

Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance during pregnancy and is recognized in almost 8.3% of pregnancies worldwide [1, 2]. GDM is recognized based on two strategies including i) 75-gram oral glucose tolerance test (OGTT) and ii) two-step 50-gram and 100-gram (OGTT) [3]. In women with higher GDM risk (obesity, age>25, familial diabetes background and North American or Asian or Latina ethnicity), the glucose intolerance screening is performed during 24-28 weeks of pregnancy [4].

Generally, GDM treatment mainly relies on insulin and medical nutrition therapy [5]. However, the use of metformin is reported to be beneficial and non-toxic in some studies [5]. It has also recommended that when insulin or metformin is available, glibenclamide should not be administered for GDM treatment [6]. Additionally, metformin alone or in combination with insulin has been reported to be a safe and more acceptable therapeutic agent compared to insulin in GDM patients with insulin therapy indication; however, long-term follow up is strictly needed to prove the long-term safety of the drug [7].

In recent years, different studies have indicated the association of thyroid dysfunction and insulin resistance as the main cause of diabetes [8]. Handisurya et al. [9] and Stanicka et al. [10] have also indicated that hypothyroidism makes glucose molecules inaccessible to insulin. Anti-thyroperoxidase (TPO) is one of the main thyroid auto-antibodies which is a diagnostic marker in Hashimoto's and Grave's disease as thyroid auto-immune diseases [11]. However, pieces of evidence indicating the correlation

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between thyroid autoantibodies and GDM are controversial [12]. In a study conducted by Shahabzian et al. [12] no significant statistical differences were observed in anti-TPO titer between diabetic and non-diabetic pregnant women. In contrast, Agarwal et al. [13] reported a higher incidence of hypothyroxinemia and Anti TPO titer in GDM patients.

Regarding the high prevalence of GDM in pregnant individuals and its complicated clinical outcomes on the mother and fetus health, this study aimed to compare the GDM therapeutic methods between positive and negative anti-TPO patients.

Patients and Methods

Patients

One hundred and two patients aged from 20 to 30 were enrolled in this cross-sectional study. The patients' GDM was confirmed by fasting blood glucose (FBG) and 75-gram OGGT test and after TSH and anti-TPO evaluation, patients were divided into two anti-TPO (+) (n=52) and anti-TPO (-) (n=50) groups. Overt hypo or hyperthyroidism, creatinine level≥1.4 mg/dl, congestive heart failure (CHF) manifestation, and liver diseases were considered as exclusion criteria. Insulin therapy was initially designated for patients with FBG higher than 105 mg/dl and diet or metformin therapy was administered to the remaining individuals regarding the FBG levels. The clinical features and FBG levels of the patients were then followed up for one week. In patients with uncontrolled FBG, the therapeutic method was changed from diet to metformin therapy or metformin to insulin/insulin+metformin therapy. Repetitive FBG evaluation and patients follow up were strictly performed until the last week of pregnancy. This study was approved by the local ethics committee of Tabriz University of Medical Sciences (Code: IR.TBZMED.REC.1396.983). Written informed consent was obtained from all participants before any action. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

Statistical Analysis

Data were analyzed using SPSS 17 software. A chi-square test was used for the correlation analysis of the qualitative variable. $P<0.05$ were considered as statistically significant.

Results

General Characteristics of the Patients

Patients were divided into anti-TPO (+) and anti-TPO (-) groups with the average age of 25.52±3.35 and 26.28±3.53, respectively. Table 1 shows the general characteristics of the groups. As it is presented, no significant differences were observed in body mass index (BMI) (p=0.065), thyroid-stimulating hormone (TSH) (p=0.4) and free T_4 (FT_4) (p=0.93) levels between groups.

Comparison of the FBG, 1 hour BS and 2 hour BS in Patients Understudy before Treatment

Table 2 represents the FBS, 1 hour BS and 2 hour BS in the studied group before the intervention. As it is shown, significant differences were observed in mentioned parameters between groups (p=0.003, p=0.041 and p=0.007 for FBS, 1 hour BS and 2 hour BS, respectively).

Therapeutic Methods Frequency in Patients Understudy

Based on therapeutic methods, patients were also classified into three groups including diet (67.6%), metformin (19.6%) and insulin/insulin+metformin (12.7%) therapy. As it is shown in Table 3, significant differences were observed in insulin/insulin+metformin (p=0.026) and diet (p=0.03) therapy. No significant statistical differences were observed in metformin therapy between groups (p=0.24).

Discussion

GDM is characterized as glucose tolerance disorder which occurs during pregnancy and is associated with increased feto-maternal morbidity and chronic mother and child-related complications [14]. Thus, screening and diagnosis of this metabolic disease are very crucial for the mother and child health [15]. Pregnant women have a higher erythrocyte turnover which renders the glycosylated hemoglobin (HbA1c) inadequate for full screening and disease onset interpretation. However, a 2-h 75g OGTT test during weeks 24-28 of pregnancy has been recommended by the European Association for the Study of Diabetes, International Association of Diabetes and Pregnancy Study Group (IADPSG), ADA and World Health Organization (WHO) [16]. The GDM prevalence in different areas of Iran has also been reported between 4.7-7.4% according to the new American Diabetes Association (ADA) [17].

Compared to the general population, a higher prevalence of thyroid disorders is observed in diabetic patients. Because patients with one organ autoimmune disorders are at risk of other organs autoimmune disorders development [18]. Olivieri A et al. [19] in a study reported a higher risk of being anti-TPO positive during pregnancy in women with a familial history of type 2 diabetes. Additionally, in a study conducted by the same author, anti-TPO titer was significantly higher in cord blood of type 1 diabetic pregnant women at the delivery with higher islet cell autoimmunity (ICA) titer in a Sardinian population [20].

Regarding the GDM patients, Agrawal M et al. [13] reported no statistically significant differences in anti-TPO positive prevalence among GDM or non-GDM pregnant women. However, in a study conducted by Vitacolonna et al. [21] a significant increase in thyroid autoimmunity was reported in pregnant women which were previously affected by GDM. Although, this increased prevalence was not associated with the development of glucose intolerance after delivery.

In the present study significantly higher FBG, 1 hour BS and 2 hour BS were observed in anti-TPO positive GDM patients compared to the anti-TPO negative counterparts. Varim C et al. [22] in their study also reported a higher fasting blood glucose (p=0.006) and insulin levels (p=0.011) in Hashimoto's anti-TPO positive patients compared to the healthy controls. In Mazaheri T et al. [23] study, no significant differences were observed in serum insulin, glucose and lipid concentration between Hashimoto's and post-ablation hypothyroidism patients. However, patients with highly positive anti-TPO antibodies exhibited increased fasting insulin levels compared to patients with lower anti-TPO titer and no autoimmune background.

Cytokines are soluble proteins that are implicated in immune response regulation [24]. They initiate the immune responses via B and T cells stimulation [24]. Recent studies have reported the presence of pro-inflammatory cytokines including interleukin (IL)-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-14, tumor necrosis factor (TNF)-α, and interferon (INF)-γ in thyroid follicular cells [25]. Under cell-mediated immunity and the presence of antigen, macrophages and T cells will be differentiated into T- helper cells which can produce a variety of pro-inflammatory cytokines [26]. In their study, Nanba et al. [27] reported an increased T-helper1 in overt Hashimoto's disease when compared to mild counterparts. Figureoavega et al. [28] also reported elevated levels of IL-17, IL-22 (as pro-inflammatory cytokines) in Hashimoto's than that of Grave's patients. Murthy K.A et al. [29] also reported a significantly higher TNF-α, IL-6, and IL-8 in pregnant women with GDM. In their study, Ategbo J.M et al. [30] also reported a higher level of IL-6, IL-10 and TNF-α cytokines in gestational diabetic mothers when compared to the controls.

Pregnant women with GDM can be managed by non-medical methods including nutrition therapy. However, many GDM cases need simultaneous insulin management [31]. Our data showed significantly higher insulin/insulin+metformin therapy frequency in GDM anti-TPO positive patients compared to the anti-TPO negative counterparts. In contrast, the frequency of diet therapy was significantly higher in GDM anti-TPO negative patients. Regarding the higher fasting blood glucose and insulin levels in anti-TPO positive patients with autoimmune thyroid disorders [22, 23], the insulin-based treatments seem to exhibit an effective outcome on glycemic control in GDM patients.

Conclusion

Our data revealed a higher FBS, 1 hour BS and 2 hours BS mean in GDM anti-TPO(+) patients compared to anti-TPO (-) counterparts. Additionally, higher insulin/insulin+metformin therapy and higher diet therapy frequency were observed in anti-TPO(+) and anti-TPO(-) GDM patients, respectively, indicating the association of anti-TPO antibodies with the GDM severity.

Conflict of interests

The authors declared that there was no conflict of interest.

References

1. Dirar AM, Doupis J. Gestational diabetes from A to Z. World journal of diabetes. 2017 Dec 15;8(12):489.
2. Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG: An International Journal of Obstetrics & Gynaecology. 2017 Apr;124(5):804-13.
3. Rani PR, Begum J. Screening and diagnosis of gestational diabetes mellitus, where do we stand. Journal of clinical and diagnostic research: JCDR. 2016 Apr;10(4):QE01.
4. Fahami F, Torabi S, Abdoli S. Prediction of glucose intolerance at 24-28 weeks of gestation by glucose and insulin level measurements in the first trimester. Iranian journal of nursing and midwifery research. 2015 Jan;20(1):81.
5. Kelley KW, Carroll DG, Meyer A. A review of current treatment strategies for gestational diabetes mellitus. Drugs in context. 2015;4.
6. Song R, Chen L, Chen Y, Si X, Liu Y, Liu Y, Irwin DM, Feng W. Comparison of glyburide and insulin in the management of gestational diabetes: a meta-analysis. PloS one. 2017;12(8).
7. Tertti K, Ekblad U, Vahlberg T, Rönnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. The review of diabetic studies: RDS. 2008;5(2):95.
8. Dimitriadis G, Mitrou P, Lambadiari V, Boutati E, Maratou E, Panagiotakos DB, Koukkou E, Tzanela M, Thalassinos N, Raptis SA. Insulin action in adipose tissue and muscle in hypothyroidism. The Journal of Clinical Endocrinology & Metabolism. 2006 Dec 1;91(12):4930-7.
9. Handisurya A, Pacini G, Tura A, Gessl A, Kautzky-Willer A. Effects of T4 replacement therapy on glucose metabolism in subjects with subclinical (SH) and overt hypothyroidism (OH). Clinical endocrinology. 2008 Dec;69(6):963-9.
10. Stanická S, Vondra K, Pelikánová T, Vlček P, Hill M, Zamrazil V. Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. Clinical Chemistry and Laboratory Medicine (CCLM). 2005 Jul 1;43(7):715-20.
11. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Frontiers in immunology. 2017 May 9;8:521.
12. Shahbazian H, Shahbazian N, Baniani MR, Yazdanpanah L, Latifi SM. Evaluation of thyroid dysfunction in pregnant women with gestational and pre-gestational diabetes. Pakistan journal of medical sciences. 2013 Apr;29(2):638.
13. Agarwal MM, Dhatt GS, Punnose J, Bishawi B, Zayed R. Thyroid function abnormalities and antithyroid antibody prevalence in pregnant women at high risk for gestational diabetes mellitus. Gynecological Endocrinology. 2006 Jan 1;22(5):261-6.
14. Jovanovic L, Pettitt DJ. Gestational diabetes mellitus. Jama. 2001; 286 (20): 2516-18.
15. Kampmann U, Madsen LR, Skajaa GO, Iversen DS, Moeller N, Ovesen P. Gestational diabetes: a clinical update. World journal of diabetes. 2015 Jul 25;6(8):1065.
16. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. PloS one. 2014;9(6).
17. Shahbazian HB, Shahbazian N, Yarahmadi M, Saiedi S. Prevalence of gestational diabetes mellitus in pregnant women referring to gynecology and obstetrics clinics. 2012: 113-121.
18. AFKHAMI AM, Rashidi M, SHOJA AA. Evaluation of thyroid autoantibodies in type 2 diabetes. 2009: 1-4.
19. Olivieri A, Valensise H, Magnani F, Medda E, De Angelis S, D Archivio M, Sorcini M, Carta S, Baccarini S, Romanini C. High frequency of antithyroid autoantibodies in pregnant women at increased risk of gestational diabetes mellitus. European journal of endocrinology. 2000 Dec 1;143(6):741-7.
20. Olivieri A, Pinna G, Lai A, Velluzzi F, Pilo A, Atzeni F, Guaita G, Pelligra I, Cirillo R, Sorcini M, Carta S. The Sardinian Autoimmunity

Study. 4. Thyroid and islet cell autoantibodies in Sardinian pregnant women at delivery: A cross-sectional study. Journal of endocrinological investigation. 2001 Sep 1;24(8):570-4.
21. Vitacolonna E, Lapolla A, Di Nenno B, Passante A, Bucci I, Giuliani C, Cerrone D, Capani F, Monaco F, Napolitano G. Gestational diabetes and thyroid autoimmunity. International journal of endocrinology. 2012;2012.
22. Varim C, Kaya T, Varim P, Nalbant A, Vatan MB, Yaylaci S, Gokosmanoglu F, Tamer A. Insulin resistance in the patients with euthyroid Hashimoto thyroiditis. 2017.
23. Mazaheri T, Sharifi F, Kamali K. Insulin resistance in hypothyroid patients under Levothyroxine therapy: a comparison between those with and without thyroid autoimmunity. Journal of Diabetes & Metabolic Disorders. 2014 Dec 1;13(1):103.
24. Gianoukakis AG, Smith TJ. The role of cytokines in the pathogenesis of endocrine disease. Can J Diabet. 2004;28(1):30-42.
25. Ganesh BB, Bhattacharya P, Gopisetty A, Prabhakar BS. Role of cytokines in the pathogenesis and suppression of thyroid autoimmunity. Journal of Interferon & Cytokine Research. 2011 Oct 1;31(10):721-31.
26. Al-Jameil N, Khan MF, Al-Rashid M, Tabassum H. Thyroid dysfunction: an autoimmune aspect. International journal of clinical and experimental medicine. 2015;8(5):6677.
27. Nanba T, Watanabe M, Inoue N, Iwatani Y. Increases of the Th1/Th2 cell ratio in severe Hashimoto's disease and in the proportion of Th17 cells in intractable Graves' disease. Thyroid. 2009 May 1;19(5):495-501.
28. Figueroa-Vega N, Alfonso-Perez M, Benedicto I, Sanchez-Madrid F, Gonzalez-Amaro R, Marazuela M. Increased circulating pro-inflammatory cytokines and Th17 lymphocytes in Hashimoto's thyroiditis. The Journal of Clinical Endocrinology & Metabolism. 2010 Feb 1;95(2):953-62.
29. Murthy KS, Bhandiwada A, Chandan SL, Gowda SL, Sindhusree G. Evaluation of oxidative stress and proinflammatory cytokines in gestational diabetes mellitus and their correlation with pregnancy outcome. Indian journal of endocrinology and metabolism. 2018 Jan;22(1):79.
30. Atègbo JM, Grissa O, Yessoufou A, Hichami A, Dramane KL, Moutairou K, Miled A, Grissa A, Jerbi M, Tabka Z, Khan NA. Modulation of adipokines and cytokines in gestational diabetes and macrosomia. The Journal of Clinical Endocrinology & Metabolism. 2006 Oct 1;91(10):4137-43.
31. Magon N, Seshiah V. Gestational diabetes mellitus: insulinic management. The Journal of Obstetrics and Gynecology of India. 2014 Apr 1;64(2):82-90.

Table 1. General characteristics of the patients.

	Anti-TPO (+) (n=52)	Anti-TPO (-) (n=50)	p
Age (year)	25.52±3.35	26.28±3.53	0.263
BMI (kg/m^2)	26.67±4.08	25.22±3.63	0.065
TSH (mIU/L)	1.37±0.72	1.26±0.6	0.4
FT$_4$ (ng/mL)	1.03±0.19	1.02±0.21	0.93

Data are presented as mean ± standard division (SD). BMI: body mass index; TSH: thyroid stimulating hormone; FT$_4$: free T$_4$.

Table 2. Comparison of FBG, 1 hour BS and 2 hour BS levels after 75-gram OGTT test before treatment in studied groups.

	Anti-TPO (+) (n=52)	Anti-TPO (-) (n=50)	p
FBG (mg/dl)	97.4±13.47	90.42±9.62	0.003
1 hour BS (mg/dl)	202.94±30.71	191.86±22.39	0.041
2 hour BS (mg/dl)	158.62±24.42	147.64±14.40	0.007

Data are presented as mean ± standard division (SD). FBS: fasting blood sugar.

Table 3. Frequency of therapeutic methods between groups.

	Anti-TPO (+) (n=52)	Anti-TPO (-) (n=50)	p
Insulin/Insulin+metformine	10 (19.2%)	3 (6%)	0.026
Metformin	13 (25%)	7 (14%)	0.24
Diet	29 (55.8%)	40 (80%)	0.03

Data are presented as number (%).