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Association between variations of physiological prolactin serum levels and the risk of type 2 diabetes: A systematic review and *meta*-analysis

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ABSTRACT

Aim: To determine the pooled association between variations of prolactin serum levels within the physiological range and the risk of type 2 diabetes mellitus (T2D).
Methods: Pubmed, Scopus, Web of Science, and grey literature were searched for studies investigating the association between variations of prolactin serum levels in the normal range and the risk of T2D in adults. The risk of prevalent and incident T2D was summarized as the odds ratio or relative risk according to the quartile of prolactin serum concentration, using random-effects *meta*-analysis.
Results: Of 2,014 articles identified, 6 met the inclusion criteria. Data were pooled from cross-sectional studies including 6,670 subjects and longitudinal studies involving 13,203 subjects. Men with prolactin levels in the fourth quartile versus those in the first quartile had decreased risk of prevalent T2D (OR 0.52; 95%CI 0.35–077). The same association was seen in women (OR 0.46; 95%CI 0.30–0.73). Conversely, prolactin levels in the fourth versus first quartile were not associated with the risk of incident T2D in men (RR 1.21; 95%CI 0.79–1.87) or women (RR 0.77; 95%CI 0.48–1.22).
Conclusion: Higher prolactin serum levels within the normal range were associated with reduced risk of prevalent but not incident T2D. Further studies are necessary to address whether this association is causal, but these findings raise the discussion regarding the optimal level of prolactin suppression in subjects undergoing therapy with dopaminergic agonists.

1. Introduction

Prolactin is a polypeptide hormone named for its lactogenic properties. However, there is increasing evidence that it is a pleiotropic factor with over 300 biological functions described to date. These include control of water and electrolytic balance, cell growth, angiogenesis, immune function, behavior, in addition to neuroprotection and interference with the

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action of other hormones, such as glucocorticoids [1]. The appearance of the genes encoding prolactin and its receptor precedes the appearance of mammals, indicating that its original function was not to promote lactation and that the latter function evolved subsequently in evolution. Indeed, it is largely believed that the primordial function of prolactin was to regulate energy metabolism and water and electrolyte balance in teleost fish [1–3].

Findings from clinical studies indicate an increased risk of type 2 diabetes mellitus (T2D) among subjects with prolactinomas [4,5] or other causes of pathological hyperprolactinemia [6]. This is most likely related to the negative effect of pathological hyperprolactinemia on post-prandial insulin sensitivity [7]. Despite the action of prolactin on beta cells to enhance glucose-induced insulin secretion, increased insulin resistance leads to diminished gluconeogenesis inhibition in the liver, diminished lipolysis inhibition in adipose tissue, and impairment of peripheral glucose uptake [8–11]. Accordingly, a study involving hyperinsulinemic-euglycemic clamp showed that obese and non-obese subjects with hyperprolactinemia exhibited post-prandial hyperinsulinemia and a significant decrease in peripheral insulin sensitivity [7].

An additional mechanism underlying dysregulation of glucose homeostasis in the setting of hyperprolactinemia is diminished adiponectin expression in adipose tissue [12,13], leading to reduced fatty acid oxidation in muscle and diminished fatty acid uptake by hepatocytes, which negatively affect insulin sensitivity [12,14,15]. Conversely, hyperprolactinemia treatment with dopaminergic agonists improves metabolic homeostasis and reduces the risk of T2D [13,15–17].

Interestingly, data from cell-based and animal studies suggest that at physiological concentrations, prolactin exhibits protective actions on beta cells [18–20]. Recombinant prolactin improves beta-cell survival in culture by diminishing apoptosis [19]. There is also evidence that prolactin upregulates insulin gene transcription and reduces the setpoint for glucose-induced insulin synthesis by stimulating glucokinases [20–22]. Moreover, low-dose prolactin administration to diabetic rats improves beta-cell function and insulin sensitivity [23]. Even higher but physiological levels of prolactin, such as those occurring in pregnancy, are considered metabolically favorable. Indeed, increased prolactin secretion during pregnancy and lactation is viewed as part of a homeostatic adaptation to the unique metabolic demands of the mother and offspring rather than simply diabetogenic. Findings from prolactin receptor knockout mice indicate that prolactin signaling is critical for beta-cell expansion during pregnancy and protection against gestational diabetes [24,25]. In addition, lower levels of prolactin during pregnancy predict a higher risk for the development of postpartum diabetes in humans [26].

Previous findings, therefore, suggest that in physiological conditions prolactin protects against T2D, but at high concentrations in pathological settings, it increases the risk of developing the disease. In this setting, we conducted a systematic review and *meta*-analysis to investigate the association between variations of prolactin serum levels in the physiological range and the risk of prevalent or incident T2D in men and nonpregnant women.

2. Methods

2.1. Protocol and registration

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [27] and registered in the Prospective Register of Systematic Reviews (PROSPERO), under the registration number CRD-139967.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

The study question of this review was created using the PECOS acronym (population, exposure, comparison, outcome, and type of studies). P was “men and non-pregnant women aged over 18 years with normal prolactin serum levels”; E was “prolactin serum levels in the fourth quartile”; C was “prolactin serum levels in the first quartile”; O was “prevalent or incident type 2 diabetes”, and S was “observational studies”. Accordingly, the inclusion criteria were observational studies that compared the prevalence or incidence of type 2 diabetes in adults with prolactin serum levels in the fourth quartile with those in the first quartile of the normal range, without publication time or language restrictions. T2D was defined by fasting blood glucose, 2-hour post glucose values from an oral glucose tolerance test, or glycated hemoglobin levels, according to the American Diabetes Association for the diagnosis and classification of diabetes [28].

2.2.2. Exclusion criteria

Reviews, case reports, case series, book chapters, and conference abstracts were excluded. Observational studies including participants with hyperprolactinemia, or taking medications known to affect serum prolactin levels, were excluded. Studies comparing prolactin serum levels between subjects with T2D and normal glucose tolerance that did not provide measures for the association serum prolactin levels and the risk of T2D were also excluded.

2.3. Search strategy and study selection

The following electronic databases were searched: PubMed, Scopus, and Web Of Science; additional search of the grey literature was conducted on Google Scholar. Databases were searched from inception to April 5, 2020, using the search terms related to exposure (“prolactin”) and the outcome of interest (“diabetes”). The search strategy described in Supplementary Table 1.

We performed manual searches across reference lists of included studies. A reference management software (Review Manager 5.3) was used to collect references and exclude duplicate studies.

Studies were selected in a two-phase process. In the first phase, two reviewers (L.F.C.; A.A.S.) independently screened the titles and abstracts from the retrieved articles to identify eligible studies. In the second phase, the same two reviewers assessed the full texts of the studies selected in the first phase and applied the same eligibility criteria. In both phases, any

disagreements were resolved by discussion with a third reviewer (A.A.A.).

2.4. Data collection process

The following information was collected from the included studies: author, year of publication, sample size, age range, gender, prevalence and incidence of T2D, confounding factors, main findings, and study design.

2.5. Risk of bias between studies

The risk of bias of included studies was assessed independently by two reviewers (L.F.C.; A.A.S.) using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies and Case-Control Studies [29], and disagreements were resolved by discussion with a third reviewer (A.A.A.). Studies were considered as having a high risk of bias when they reached 49% or less of the score "yes", as having a moderate risk of bias when it reached between 50% and 69% of the score "yes", and as having a low risk of bias when it reached 70% or more of the score "yes". Decisions about scoring were agreed upon by reviewers previously to study assessment.

2.6. Summary measures

The odds ratio or relative risk of T2D in subjects with prolactin serum levels in the fourth quartile versus serum levels in the first quartile, and its 95% confidence intervals, were the main outcome measures.

2.7. Results of individual studies (qualitative synthesis)

The extracted data from individual studies were presented in a table format and their main conclusions described.

2.8. Synthesis of results (meta-analysis)

The adjusted estimates from individual studies comparing the risk of prevalent or incident T2D between men and women with serum prolactin levels in the fourth quartile and those with serum prolactin levels in the first quartile (ref-

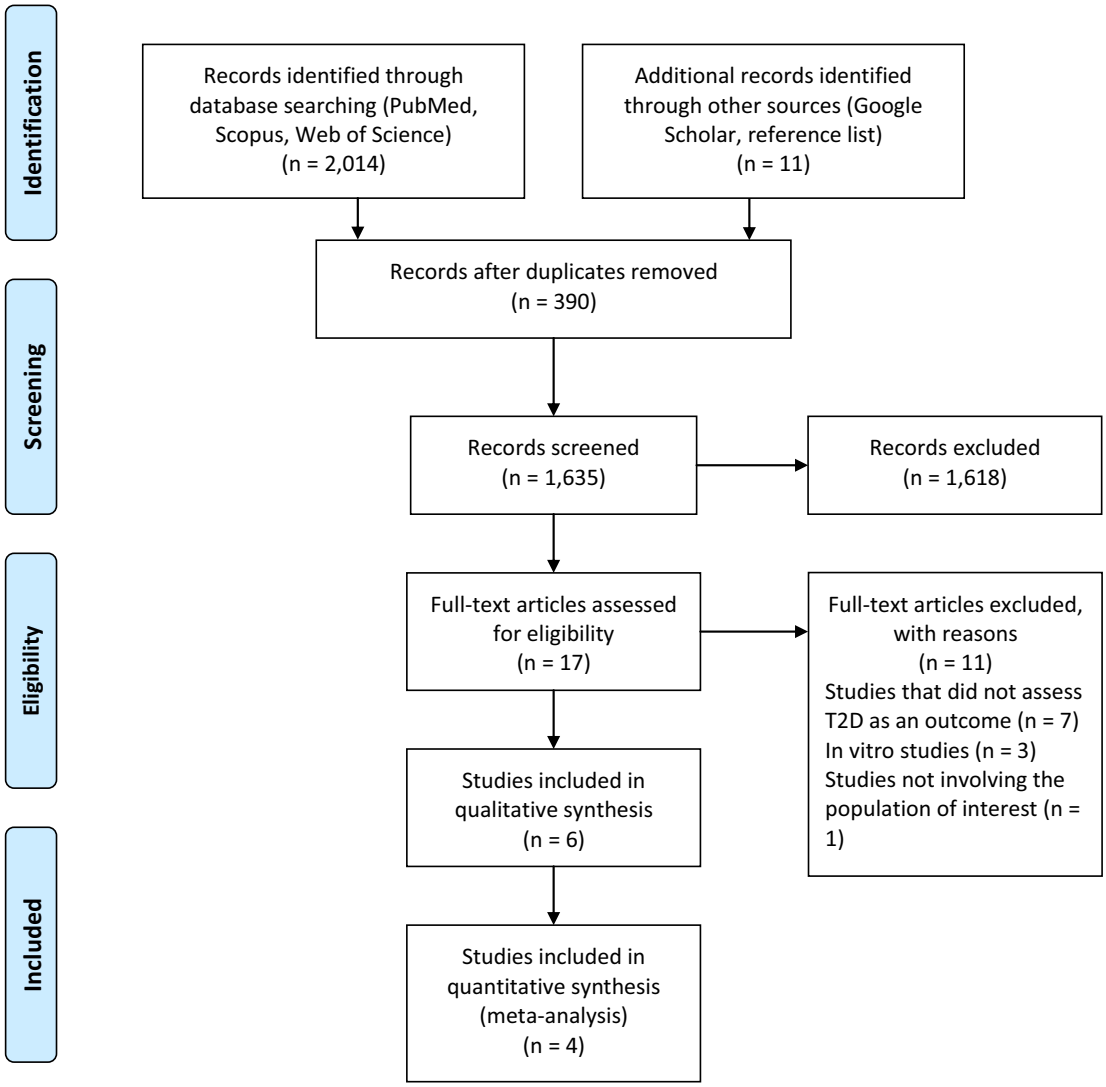

Fig. 1 – Flow diagram of literature search and study selection process. Adapted from [27]

erence category), defined for the study population, were pooled using random effect *meta*-analysis. For studies reporting the measure of association considering the fourth quartile of serum prolactin levels as the reference category, the reciprocal measure was calculated. Heterogeneity was assessed by the I^2 test. We reported the results as the odds ratio or relative risk, with 95% confidence intervals. Statistical significance was considered when $p < 0.05$. All analysis was conducted using RevMan statistical software 5.1.

3. Results

3.1. Study selection

A total of 2,014 citations were identified, and 17 were selected based on their titles and abstracts for detailed assessment (Fig. 1). Eleven studies were excluded (Supplementary Table 2), and 6 studies met the inclusion criteria and remained for final analysis [30–35]. Data from 5 of them were pooled in the *meta*-analysis [31–34].

3.2. Study characteristics

The studies were conducted in the United States [30,34], China [32,33], Germany [35], and India [31], and published between 2013 and 2019, in English. Two studies were cross-sectional [31,36], three were prospective [30,32,34], and one had both cross-sectional and prospective components [35]. Sample size ranged from 300 to 8,615 subjects, and most studies including men and women reported the measures of association for each gender separately. In all studies, prolactin serum levels were determined by chemiluminescence immunoassay. Data was presented adjusted by relevant factors for T2D risk in all studies, and the most frequent adjustment confounders were age, body mass index, smoking status, and family history of T2D. In all but two studies [30,34], the first quartile of serum prolactin levels was considered the reference for determining the measures of association between prolactin levels and T2D risk.

3.3. Risk of bias within studies

All included studies were considered as having a low risk of bias (Supplementary Table 3).

3.4. Results of individual studies (qualitative synthesis)

The summary of the characteristics of the included studies is shown in Table 1. Three studies assessed the association between prolactin serum levels in the physiological range and the risk of prevalent T2D [31,33,35]. All three reported that higher prolactin serum levels were associated with reduced risk of prevalent T2D. In one of them, involving the smaller sample (n = 300), the association was observed only in women.

Four studies examined the association between prolactin serum levels in the physiological range and the risk of incident T2D [30,32,34,35]. Two studies found no association between prolactin levels and the risk of incident T2D [30,35], and two reported that higher prolactin serum levels reduced the risk of developing T2D among women [32,34]. Among the two later studies, one included both male and female [32] and one included only female subjects [34]. Notably, both studies that found no association between prolactin serum levels and the risk of incident T2D involved younger women (mean age of around 40 [30] and 49.5 years [35]) and a shorter follow-up time (5 to 6 years). Conversely, both studies that reported that higher prolactin levels in the normal range protected against subsequent development of T2D assessed incident diabetes in older women. One study included postmenopausal women, with the mean age of 60 years, and examined the incidence of T2D after a mean 4-year follow-up [32]. The other included women with a mean age of 49 years, but assessed incident T2D after a longer follow-up time, of 22 years [34].

One study was excluded from the *meta*-analysis because it did not report the data considering the first quartile of prolactin serum levels as the reference category [35].

Four studies assessed the risk of impaired glucose regulation (impaired fasting glucose or impaired glucose tolerance) and metabolic syndrome, in addition to T2D. Wang et al. (2013) found that higher normal prolactin levels were associated with reduced risk of prevalent impaired glucose regulation in men and women [33], whereas Chahar et al. (2016) found this association in women but not men [31]. Both Balbach et al. (2013) and Therkelsen et al. (2016) found no association between variations in normal serum prolactin levels and the occurrence of metabolic syndrome [30,35].

Eight studies were excluded because they assessed outcomes other than prevalent or incident T2D. It is noteworthy that they indicated that higher normal serum prolactin levels were associated with more favorable metabolic endpoints, or that prolactin serum levels within the physiological range were lower among subjects with T2D when compared with those with normal glucose tolerance (Supplementary Table 2).

3.5. Synthesis of results (meta-analysis)

Data from 6,670 subjects (3,241 male, 3,429 female) were pooled in the *meta*-analysis of the association between prolactin serum levels and prevalent T2D, and data from 13,203 subjects (2381 male, 10,822 female) were pooled in the *meta*-analysis of the association between prolactin serum levels and incident T2D.

Prolactin serum levels were significantly associated with lower likelihood of prevalent T2D (Fig. 2), with an overall odds ratio of 0.50 (CI95%: 0.39–0.65, $p < 0.00001$). Subgroup analysis indicated that the association was significant in both men (odds ratio: 0.52, CI95%: 0.35–0.77, $p = 0.0009$) and women (odds ratio: 0.46, CI95%: 0.30–0.73, $p = 0.0009$).

Prolactin serum levels were not significantly associated with the risk of incident type 2 diabetes (Fig. 3), with an overall relative risk of 0.90 (CI 0.63–1.28, $p = 0.56$). There was also no significant association in men (relative risk: 1.21, CI: 0.79–1.87, $p = 0.38$) or women (relative risk: 0.77, CI: 0.48–1.22, $p = 0.26$) considered as subgroups.

Table 1 – Summary of the characteristics of included studies (n = 6).

Author (year); country; study design	Sample size; gender; mean/median[1] age (y)	Adjustment confounders	Outcomes	OR or RR/HR (95%CI)	Conclusion
Wang et al. (2013); China, cross-sectional	2,377; male (n = 1,034) and female (n = 1,343); mean 58.3 ± 8.8 to 64 ± 9.8, men; 61.6 ± 8.2 to 63.5 ± 10, men	Age, smoking status, alcohol drinking status, BMI, family history of T2D	T2D IGR	Q4 vs Q1 (Q1 referent) Men: OR 0.38 (0.24–0.59) Women: OR 0.47 (0.32–0.70) Q4 vs Q1 (Q1 referent) Men: OR 0.54 (0.33–0.89) Women: OR 0.54 (0.36–0.81)	Higher prolactin serum levels within the normal range were associated with reduced odds of T2D and IGR
Balbach et al. (2013); Germany; cross-sectional and longitudinal (5-year follow up)	Cross-sectional: 3,993; male (n = 2,027) and female (n = 1,966) Longitudinal: 3,078; male (n = 1,489) and female (n = 1,589) Median 52.1 (37.4–65.3) y, men; 49.5 (36–62.3) y, women (from SHIP Cohort)	Age and smoking status	T2D Metabolic syndrome	Q1 vs Q4 (Q4 referent) Cross-sectional Men: OR 1.55 (1.13–2.14) Women: OR 1.70 (1.1–2.62) Longitudinal Men: RR 0.78 (0.45–1.35) Women: RR 0.73 (0.37–1.43) Q1 vs Q4 (Q4 referent) Cross-sectional Men: OR 1.15 (0.98–1.35) Women: OR 1.11 (0.89–1.39) Longitudinal Men: RR 0.87 (0.68–1.53) Women: RR 0.87 (0.68–1.10)	Higher prolactin serum levels within the normal range were associated with reduced risk of prevalent but not incident diabetes or metabolic syndrome
Wang et al. (2016); China, longitudinal (4-year follow-up)	1,510; male (n = 892) and female n = 618), mean age 57.5 ± 7.9 to 63.6 ± 9.9 y, men; 60.1 ± 7.8 to 61.9 ± 10 y, women Only postmenopausal females were included	Age, smoking status, BMI, family history of T2D, waist circumference, serum levels of triglycerides, LDL and HDL cholesterol (for women, additional parity and hormone therapy)	T2D	Q4 vs Q1 (Q1 referent) Men: HR 1.11 (0.55–2.21) Women: HR 0.49 (0.26–0.91)	Higher prolactin serum levels within the normal range were associated with lower incidence of T2D among post-menopausal women

Table 1 – (*continued*)

Author (year); country; study design	Sample size; gender; mean/median[1] age (y)	Adjustment confounders	Outcomes	OR or RR/HR (95%CI)	Conclusion
Therkelsen et al. (2016); United States; longitudinal (mean 6.1-year follow-up)	3,232; male (n = 1,547) and female (n = 1,685); men: 40.7 ± 8.6 y, women: 40.2 ± 8.7 (from FHS)	Age, sex (for overall risk), smoking status, menopausal status, hormone replacement therapy, BMI	T2D Metabolic syndrome	Change in at follow-up examination per 5-mg/dL increment in prolactin. Overall: RR 1.17 (0.85–1.62) Men: RR 1.51 (0.90–2.53) Women: RR 0.97 (0.64–1.48) Overall: RR 1.01 (0.86–1.19) Men: RR 1.14 (0.85–1.53) Women: RR 0.96 (0.79–1.17)	Higher prolactin serum levels within the normal range were not associated with the risk of T2D or metabolic syndrome
Chahar et al. (2016); India; cross-sectional	300; male (n = 180) and female (n = 120); 51.4 ± 4.8 to 54.4 ± 5.9 y, men; 54.4 ± 4.1 to 57.6 ± 4.9 y, women	Age, BMI, glycated hemoglobin, serum levels of triglycerides, LDL and HDL cholesterol	T2D IGR	Q4 vs Q1 (Q1 referent) Men: OR 0.55 (0.19–1.57) Women: OR 0.13 (0.03–0.56) Q4 vs Q1 (Q1 referent) Men: OR 0.61 (0.21–1.72) Women: OR 0.18 (0.04–0.74)	Higher prolactin serum levels within the normal range were associated with reduced odds of T2D in women but not in men
Li et al. (2018); United States; longitudinal (22-year follow-up)	8,615; female; mean 49.2 ± 7.6 to 56.1 ± 7.9 y (from NHS and NHSII studies)	Age, follow-up period and cohort, fasting status/time of day of blood draw, steroid/antidepressant use, menopausal status, postmenopausal hormone therapy, BMI, physical activity, AHEI score, smoking status, childhood body size, MHI-5 score, parity, age at menarche and menopause, change in menopausal status and postmenopausal hormone therapy compared with blood draw, family history of diabetes, history of hypertension and hypercholesterolemia, incident breast or ovarian cancer, incident RA	T2D	Q4 vs Q1 (Q1 referent) Women: RR 0.73 (0.55–0.95)	Higher prolactin serum levels within the normal range were associated with lower incidence of T2D

AHEI: Alternative Healthy Eating Index; BMI: body mass index; FHS: Framingham Heart Study; HDL: high-density lipoprotein; IGR: impaired glucose regulation (impaired fasting glucose and/or impaired glucose tolerance); LDL: low-density lipoprotein; MHI-5: Five-item Mental Health Inventory; NHS: Nurses' Health Study; NHSII: Nurses' Health Study II; PRL: prolactin; RA: rheumatoid arthritis; SHIP: Study of Health in Pomerania; T2D: type 2 diabetes.

[1] Mean/median age reported for subjects in each quartile of prolactin serum levels.

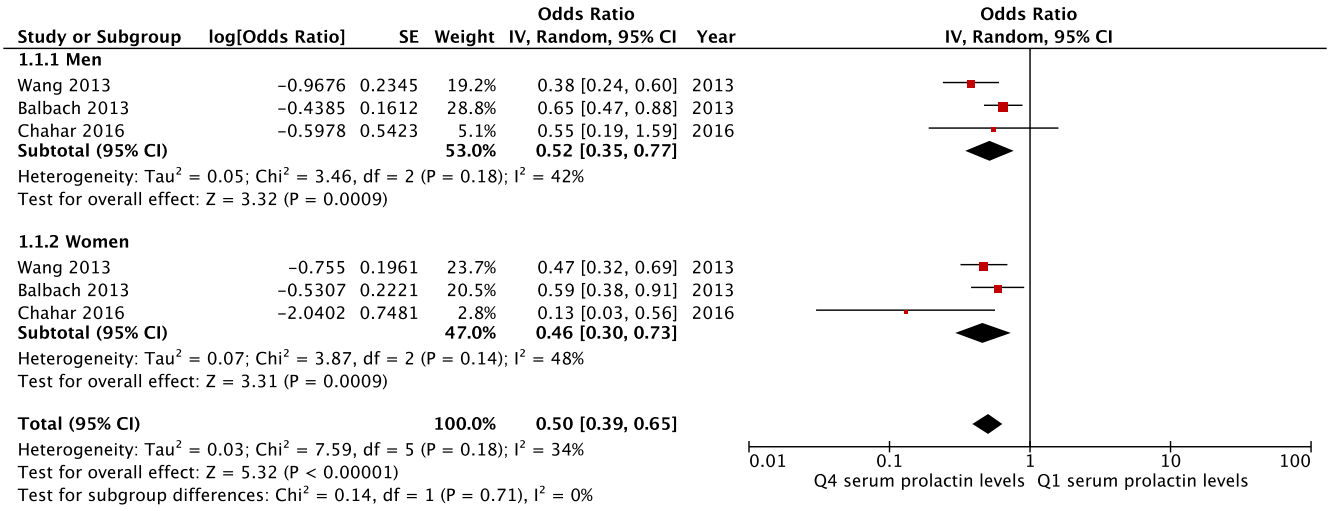

Fig. 2 – Association between prolactin serum levels and prevalent type 2 diabetes in men and women.

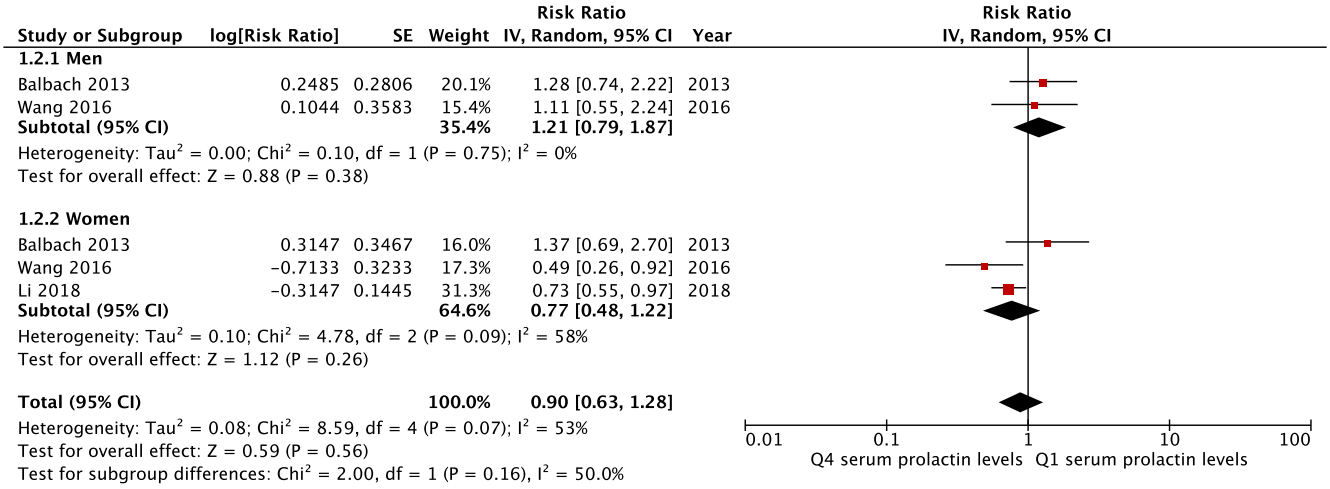

Fig. 3 – Association between prolactin serum levels and incident type 2 diabetes in men and women.

4. Discussion

Our *meta*-analysis indicates that there is a significant overall association between higher prolactin serum levels in the physiological range and reduced risk of prevalent T2D among men and women. Conversely, higher normal prolactin serum levels were not associated with reduced risk of incident T2D. To our knowledge, this is the first review assessing the association between prolactin serum levels and the risk of T2D. Despite the paucity of studies addressing this question that were retrieved after a comprehensive search, we could pool data from 20,027 subjects enrolled in five individual studies considered to have a low risk of bias and a robust methodology [31,37–39].

Three cross-sectional studies examined the association between prolactin serum levels in the physiological range and the occurrence of T2D [31,33,35]. Even though all reported reduced odds of T2D among subjects with higher prolactin concentrations, we could pool data from only two studies [31,33]. The overall *meta*-analysis indicated that higher prolactin levels were associated with reduced likelihood of T2D 0.50 (CI95%: 0.39–0.65, p < 0.00001), and subgroup analysis indicated this association was significant in both men (odds ratio: 0.52, CI95%: 0.35–0.77, p = 0.0009) and women (odds ratio: 0.46, CI95%: 0.30–0.73, p = 0.0009). It is important to point that the three included studies [31,33,35] differed with respect to the number of participants, their clinical characteristics, and the potential confounders for which the association was adjusted.

Wang et al. (2013) enrolled 1,343 postmenopausal women, with the mean age of 60 years, and found that women with prolactin levels in the higher quartile had reduced odds of T2D when compared with the lower quartile (0.47, CI95% 0.32–0.70), after adjustment for age, smoking, and alcohol drinking status, body mass index and family history of T2D [33]. Chahar et al. (2016) included only 120 women, with the mean age of 55 years. They found that those with prolactin levels in the fourth quartile had reduced odds of T2D when compared with the lower quartile (0.13, CI95% 0.03–0.56), after adjustment for age, body mass index, glycated hemoglobin,

and serum lipid levels [31]. The study from Balbach et al. (2013) also reported a positive association between higher normal prolactin serum concentrations and diminished risk of prevalent T2D. The authors enrolled 1,966 women with the mean age of 52 years and found that those with lower prolactin levels had increased odds of T2D occurrence (OR 1.7, CI95% 1.1–2.62), after adjustment for age and smoking status [35]. Altogether, these findings point to the inverse association between higher physiological prolactin serum levels and the likelihood of T2D occurrence.

Four longitudinal studies addressed whether variations in prolactin serum concentrations in the normal range were associated with T2D risk, but their findings were varied. Qualitative analysis indicated that two studies found that higher normal prolactin levels were associated with reduced risk of incident T2D among women [32,34], whereas two studies found no association among women [30,35] and three studies found no association among men [30,32,35]. The results from three studies [32,34,35] could be pooled in the *meta*-analysis. No overall association was found between prolactin levels and incident T2D risk, and this finding was maintained after subgroup analysis on the basis of gender. Notably, the longitudinal study that was excluded from the *meta*-analysis [30] showed no association between prolactin levels in the physiological range and T2D risk.

It is noteworthy that the inconsistent findings among longitudinal studies may be attributed, at least in part, to differences in study design, particularly with respect to the age of the participants and follow-up time and, therefore, to the age at which incident T2D was assessed. Both studies that reported no association between serum prolactin and incident T2D included younger women and had a shorter follow up time compared with those that reported that higher prolactin predicted a lower incidence of T2D. Balbach et al. (2013) enrolled women with the median age of 52 years who were followed for five years to assess the development of T2D [35], and Therkelsen et al. (2016) included women with the mean age of 40 years who were followed for six years [30]. Conversely, the studies that reported the inverse association between higher normal prolactin levels involved older women [32] or women who were assessed for incident T2D after a longer follow-up time [34]. Wang et al. enrolled women with the mean age of 60 years, who were followed for four years [32], whereas Li et al. included women with the mean age of 49 to 56 years, but who were followed for twenty two years for assessment of incident T2D [34]. Therefore, women were assessed for incident T2D at an older age in both studies.

We could not conduct subgroup *meta*-analysis based on age due to the methodological differences between studies. Although in all included studies the association between the quartile of prolactin serum levels and T2D was adjusted for age, the age range of the participants varied among studies. Qualitative analysis of the studies suggested the possibility that the association between higher normal prolactin levels and reduced incidence of T2D was dependent upon age. Accordingly, a previous study indicated that the association between higher physiological prolactin serum levels and favorable measures of glucose homeostasis were age-dependent. Wagner et al. (2014) examined 1,683 subjects with normal prolactin levels and normal glucose tolerance and found an overall positive correlation between prolactin levels and glucose tolerance. In a subgroup of 494 subjects, the authors also found a positive association between prolactin and insulin sensitivity assessed by hyperinsulinemic-euglycemic clamp. Interestingly, the authors described that the association was strongly correlated with age, such that the correlation was positive only among older participants and was inverted to a negative one among younger subjects [40]. It is, therefore, plausible to speculate that the protective role of prolactin against T2D may be observed among older but not younger women.

The reasons for the influence of age on the association between prolactin serum levels and the risk of T2D are not clear. It is possible that the protective effect of prolactin could be most readily observed among older women because they have a higher risk of T2D when compared to younger women [41,42]. We can also hypothesize that the favorable central [43] and peripheral [23] effects of prolactin on glucose homeostasis may depend upon factors that change with aging since beta-cell function [44] and both peripheral [45] and central [46] insulin sensitivity are impaired with increasing age.

We could not establish a gender-specific association between prolactin serum levels and the risk of T2D. Higher prolactin levels were associated with reduced prevalent but not incident T2D among men and women. It is worth noting that previous studies have suggested sexual dimorphism in the association between prolactin concentrations and metabolic endpoints in humans and rodents, such as glucose-stimulated insulin secretion [47] and metabolic syndrome [35].

Despite the fact that our findings support an association between higher physiological prolactin serum levels of reduced T2D risk, they do not establish that this association is a causal one. Indeed, the association was found in cross-sectional but not longitudinal studies. However, evidence from animal and in vitro studies indicate that the protective role of prolactin in T2D development is biologically plausible, given that prolactin and its receptor play a key role in glucose homeostasis by favorably affecting insulin sensitivity and beta-cell function, at physiological concentrations. In cell-based studies, prolactin promotes beta-cell survival by suppressing apoptosis [19] and regulates beta-cell function [48]. In vivo, it was shown that prolactin administration to rats with high fat diet-induced obesity improved systemic insulin sensitivity in addition to preventing adipocyte hypertrophy and reducing the inflammatory response in visceral adipose tissue [49]. Consistently with the favorable effect of physiological prolactin concentrations on glucose homeostasis, low-dose prolactin administration to diabetic rats promoted increased beta-cell mass and improved hepatic liver insulin resistance, whereas high-dose prolactin treatment induced whole-body insulin resistance and impaired glucose-stimulated insulin secretion, despite increasing beta-cell mass [23]. Moreover, signaling through the prolactin receptor is critical for hepatic insulin sensitivity [50] and pancreatic insulin secretion [25].

Reduced prolactin signaling may have not only direct actions to impair metabolic homeostasis but also reflect reduced central serotoninergic activity. Serotoninergic tonus regulates several physiological processes, such as appetite,

thermogenesis, and insulin secretion, in addition to mood, fear, stress reaction, locomotion, sleep, and cardiovascular function [51]. Therefore, it is reasonable to speculate that reduced central serotoninergic activity associated with low prolactin levels also leads to worse metabolic outcomes.

It is noteworthy that findings from observational studies indicate that prolactin levels are associated with metabolic endpoints other than prevalent and incident T2D. Corona et al. (2014) reported that in over 2,900 men aged 40 to 79 years, low prolactin serum concentrations were correlated with an unhealthy metabolic phenotype and increased prevalence of metabolic syndrome, in addition to worse sexual function [52]. Daimon et al. (2017) showed that lower normal prolactin levels were associated with increased insulin resistance but no changes in insulin secretion among non-diabetic men, as indicated by HOMA-IR and HOMA-beta, respectively [53]. Ruiz-Herrera et al. (2017) showed that among male subjects with obesity higher normal prolactin serum levels were correlated with higher serum adiponectin levels [49], and Wagner et al. (2014) found that serum prolactin levels were positively correlated with insulin sensitivity and higher glucose tolerance among older subjects with normal glucose tolerance [40]. More recently, Ponce et al. (2020) described that lower prolactin levels were associated with insulin resistance and adipocyte hypertrophy in the visceral adipose tissue of overweight and obese adults [54]. In agreement with the unhealthy phenotype associated with low prolactin levels, some authors raise the interesting discussion that lower degrees of prolactin suppression in hyperprolactinemia treatment with dopaminergic agonists, with the target of maintaining prolactin levels within the physiological range, could be presumed to be safer [51,52].

This systematic review and *meta*-analysis were limited by the heterogeneity in the design of the included studies. Therefore, this precluded pooling data from all of them. Besides, we could not provide an estimate for the association between higher normal prolactin levels and the risk of incident T2D among men, neither conduct subgroup analysis based on age.

In conclusion, our findings suggest that prolactin serum levels in the fourth quartile of the physiological range, when compared with the first quartile, are associated with reduced risk of prevalent T2D among men and women. Future studies are valuable to address whether this association is a causal one and, therefore, whether prolactin serum levels represent a marker of metabolic diseases such as T2D or are causally related to the disease. Understanding this could provide insights to the discussion about target prolactin suppression for patients with hyperprolactinemia undergoing therapy with dopaminergic agonists. On longer-term, they could provide the rationale for the development prolactin signaling-based therapies for T2D.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108247.

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