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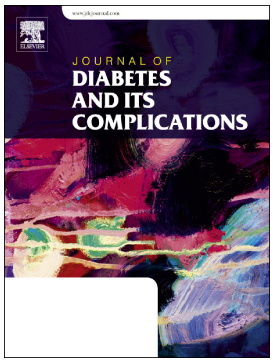

Association of detectable C-peptide levels with glycemic control and chronic complications in individuals with type 1 diabetes mellitus: A systematic review and meta-analysis

Mahin Seifi Alan, Amirhossein Tayebi, Elmira Jafari Afshar, Sanaz Seifi Alan, Mahnaz Seifi Alan, Ramina Fazeli, Tooba Sohbatzade, Parham Samimisedeh, Hadith Rastad

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Title:

Association of detectable C-peptide levels with glycemic control and chronic complications in individuals with type 1 diabetes mellitus: A systematic review and meta-analysis

Running title: Clinical outcomes of C-peptide in type 1 diabetes

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Highlights

- We have summarized the available evidence on the clinical significance of detectable levels of C-peptide in T1DM.
- A systematic search and meta-analysis were performed using online databases.
- Individuals with T1DM in the detectable C-peptide group, compared with the undetectable C-peptide group, had lower mean HbA1c (- 0.08) and daily insulin dose (- 0.41) and showed lower odds for retinopathy (pooled crude odds ratios: 0.53) and nephropathy complications (0.62).
- Individuals with T1DM in the detectable C-peptide group may experience better clinical outcomes.

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Abstract:

Aims: Multiple studies have addressed the association between detectable levels of C-peptide and glycemic control, as well as the development of chronic complications of type 1 diabetes mellitus (T1DM), including both macrovascular and microvascular diseases. We aimed to summarize the available evidence on the clinical significance of detectable levels of C-peptide in T1DM.

Method: A systematic search was performed on online databases using the following key terms: T1DM, C-peptide, diabetes mellitus complications, and glycemic parameters. We pooled standardized mean difference (SMD) and odds ratios (OR).

Results: Of the 1,519 articles retrieved from the initial search, 38 (12 cohort and 26 cross-sectional studies) met our eligibility criteria. Individuals with T1DM in the detectable C-peptide group, compared with the undetectable C-peptide group, had lower mean HbA1c [pooled SMD (95% confidence interval (95% CI)): - 0.08 (- 0.13 to - 0.02), I^2 = 0%, p.value: 0.005] and daily insulin dose [- 0.41 (- 0.65 to - 0.18), I^2 = 83%), p.value < 0.001]. They also showed lower odds for retinopathy [pooled crude OR (95% CI): 0.53 (0.41 to 0.69), I^2 = 65%, p.value < 0.001] and nephropathy complications [0.62 (0.55 to 0.70), I^2 = 19%, p.value < 0.001]; however, the two groups were similar regarding neuropathy [0.92 (0.65 to 1.31), I^2 = 0%, p.value: 0.31].

Conclusions: The available evidence suggests that individuals with T1DM in the detectable C-peptide group may experience better clinical outcomes.

Keywords: T1DM; C-peptide; glycemic control parameters; diabetes mellitus complications

1. Introduction

Type 1 diabetes mellitus (T1DM) is a condition characterized by the loss of β-cell mass in pancreatic islets caused by an autoimmune response [1]. The novel ultrasensitive method for measuring C-peptide levels allows for the detection of lower levels of this biomarker than previously possible in individuals with T1DM, even long after diagnosis [2,3].

Many studies have reported detectable levels of C-peptide in individuals with T1DM years after their initial diagnosis, indicating the presence of endogenous insulin secretion by residual autoimmune-resistant β-cells [4-6]. Previous studies have explored the risk factors and determinants associated with detectable C-peptide levels in T1DM. In this regard, some human leukocyte antigens (HLA) serotypes, including HLA DR3, DR4, and DQ8, along with early age at diagnosis, long-standing disease, higher HbA1c at the time of diagnosis, and male gender, are inversely associated with detectable C-peptide levels in individuals with T1DM [2,7].

Increasing numbers of studies have assessed whether detectable C-peptide levels are correlated with lower glucose level fluctuations and better glycemic control in individuals with T1DM[8,9]. Additionally, some studies have addressed the association between detectable C-peptide levels and chronic complications of T1DM, including macrovascular and microvascular diseases [10,11].

Nevertheless, current evidence regarding the clinical importance of detectable C-peptide levels in individuals with T1DM is scattered, making it difficult to utilize these data in clinical decision-making. Thus, as the first systematic review and meta-analysis in this area, our goal is to provide a clear and cohesive summary of the key findings from the existing evidence on the clinical significance of detectable C-peptide levels in individuals with T1DM.

2. Materials and Methods

We conducted a systematic review of the literature following a standardized methodology and reported our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Since our study was a systematic review of existing literature, we were exempt from obtaining institutional ethics committee approval. We included all original studies assessing C-peptide levels in individuals with T1DM.

2.1. Search strategy

A systematic search was conducted on online databases, including PubMed, Embase, and Scopus, on July 16, 2024, using a combination of related keywords in three domains: T1DM, C-peptide, and diabetes complications (diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, hypoglycemia, diabetic cardiomyopathy, foot ulcer, diabetic ketoacidosis (DKA), albuminuria, microalbuminuria, microaneurysms, and nerve conduction). We used the Boolean operator "OR" to connect key terms within each domain and the "AND" operator to connect the domains. In addition, we manually searched the first 100 pages of Google Scholar and the reference lists of relevant articles for any additional citations (Figure 1). We imported all citations from the retrieved documents into EndNote software (version X9.3.2, Captivate Analytics, California, USA) and removed duplicate articles.

2.2. Study selection

Two researchers (M.S1 & R.F) independently screened the titles, abstracts, and full texts of the imported articles to identify eligible studies. Any disagreements were resolved through discussion. To be included in our review study, studies had to report C-peptide levels in individuals with T1DM and meet the following criteria:

1. Individuals with T1DM
2. Presence of at least one measurement of C-peptide
3. Observational study design: cross-sectional studies, case-control, and cohort studies
4. Written in English

5. At least one of the following complications related to T1DM included in the studies: glycemic control, microvascular complications, or macrovascular complications.

Exclusion criteria

1. Animal studies, in vitro studies, and review articles

2. Not available in full text

2.3. Data extraction

We extracted the following data from the full text of the included articles into "Data extraction form" in Microsoft Excel (Version 2016, Microsoft Corp., Redmond, WA, USA): First author's name, publication year, country, study design, sample size, age, gender, BMI, time of diagnosis of T1DM, technique for assessing C-peptide, and the C-peptide levels.

2.4. Quality assessment

Two of our researchers (M.S1 & S.S) assessed the quality of the included studies independently using the Newcastle– Ottawa Scale (NOS) appraisal tool checklists adopted for each type of study design to assess the quality of the included studies. Our third researcher (H.R.) resolved any disagreements (Table 1 and 2).

2.5. Statistical analysis

We utilized either the random-effect or the fixed-effect models based on the heterogeneity size of the Standardized Mean Difference (SMD) or odds ratios (OR). The magnitude and significance of the heterogeneity were determined by I-squared statistics and Q-test, respectively. We used the random-effect model if the I-squared statistic was greater than 25%. We combined SMD and OR using inverse variance and Mantel-Haenszel methods, respectively. We computed the SMD for HbA1c and insulin dose, as well as the crude OR for retinopathy, nephropathy, and neuropathy. These calculations were performed for the comparison between the detectable and undetectable C-peptide groups among individuals with T1DM. Meta-analyses were conducted using the R Meta package in R Studio software (version 4.2.2).

3. Results

In the initial search, a total of 1,519 articles were identified. Following the removal of duplicates (238 articles) and those that did not meet the inclusion criteria based on title/abstract (1,127 articles) or full text (116 articles), 38 articles were considered eligible for this study. These 38 articles consisted of 12 cohort studies (mean/median follow-up duration of 0.5 years to 20 years) and 26 cross-sectional studies. Please refer to Figure 1 for a visual representation of this process.

Table 3 presents the characteristics of the included studies. Overall, the included studies investigated the associations between C-peptide status and glycemic control indicators (HbA1c (n = 27) [2,4,5,7,8,11-32], daily inulin dose (n = 20) [2,4,8,14-20,22,23,26-29,31-34], hypoglycemia events (n = 11) [7,15,16,20,22,25,29,31,35-37], DKA events (n = 4)[16,17,31,38], mean glucose (n = 6) [8,14,18,25,26,32], coefficient of variation (CV) (n = 7) [8,18,21,25,26,28,39], %time spent above (n = 5) [8,14,25,26,32]/below (n = 4) [8,14,21,26]/ and in range (n = 8)[8,14,18,21,26,28,32,39], glucose standard deviation (SD) (n = 2)[18,25], mean amplitude of glycemic excursions (MAGE) (n = 1)[18]), microvascular complications (overall (n = 2)[7,13] or by type: nephropathy (n = 6) [2,15,16,29,30,40], retinopathy (n = 16) [2,4,5,12,15-17,22,25,29,30,32,34,38,40-42], albuminuria (n = 6) [2,4,22,29,34,38], neuropathy (n = 6) [4,15,17,29,34,38]), and macrovascular complications (n = 5)[2,4,13,15,43], (overall, cardiovascular disease (CVD), cardiovascular event, or coronary artery disease (CAD)) in individuals with T1DM (Table 4).

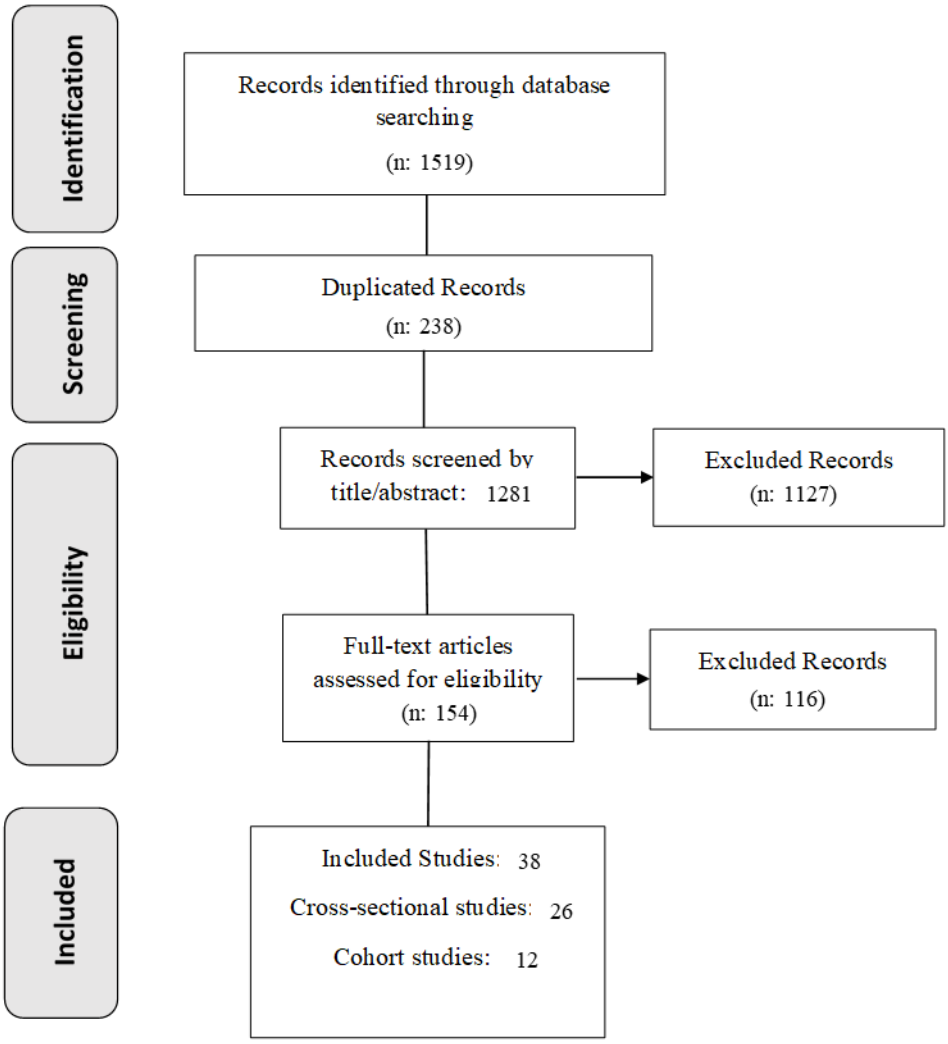


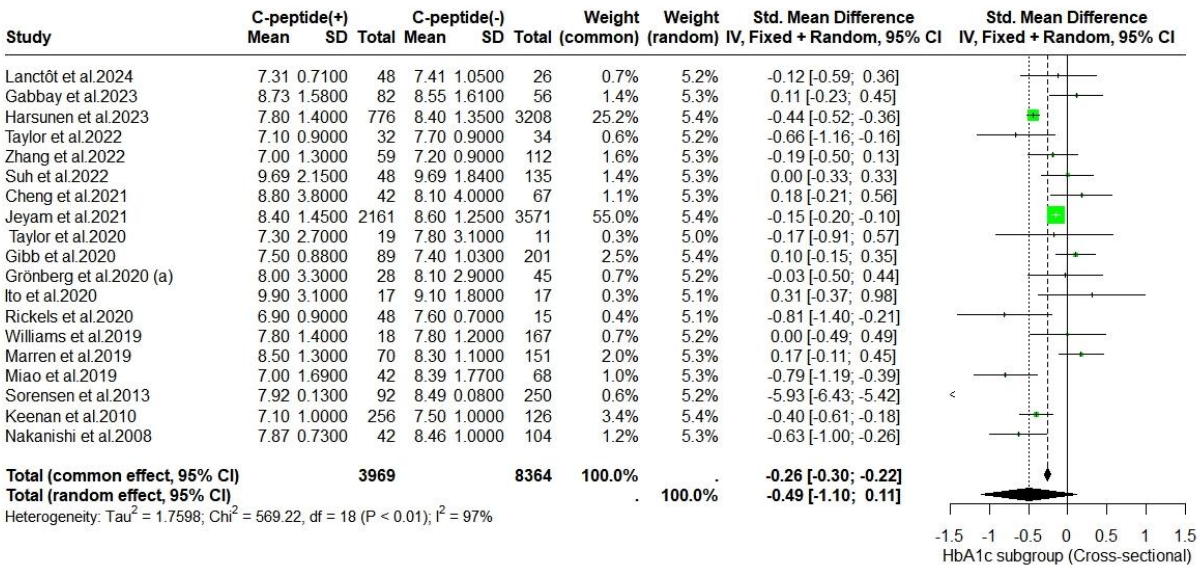
Figure 1: PRISMA Flowchart for the selection process of studies

Included studies were published between 2008 and 2024 [2,5,13,14,16,19,20,22,25,26,28,33,35-37,41]. The number of participants varied from 19 individuals in Babaya et al.'s study [39] to 5,732 in Jeyam et al.'s study [16], which were recruited using different inclusion criteria. The mean/median T1DM duration, reported by 33 studies, varies from 0 to 56 years and was lower than 20 years in 22 out of the 33 studies. In 21 studies, T1DM duration was compared between C-peptide groups, and 9 of them found a lower disease duration in individuals with T1DM in the detectable C-peptide group than in the undetectable group. Most research comparing gender (18 out 22 studies) or BMI (18 out of 20 studies) between the two groups found no significant findings in this regard.

Studies utilized different types of C-peptide tests (reported by 36 studies), including random (rCP) (n = 7) [2,5,16,24,25,35,40], fasting (fCP) (n = 11) [7,13,29-32,34,37-39,44], and stimulated (n = 13 [4,8,14,17-23,26,27,33], i.e., postprandial C-peptide (PCP), mixed meal tolerance test (MMTT), oral glucose tolerance test (OGTT), and glucagon stimulation test (GST)). Additionally, five studies utilized both fasting and stimulated methods [12,15,32,33,42], and two studies used the urinary C-peptide creatinine ratio (UCPCR) [28,43]. In addition, included studies categorized participants into two groups using different cut points for C-peptide (Table 4).

3.1. HbA1c

A total of 25 studies (6 cohorts [12,14,16-19] and 19 cross-sectional [2,4,5,7,8,13,15,20-29,31,44]) compared HbA1c between individuals with T1DM in the detectable and undetectable C-peptide groups; of those, 11 studies found a significant difference between detectable and undetectable C-peptide groups. All consistently showed that individuals with T1DM in detectable C-peptide group had a lower HbA1c [2,4,7,12,15,16,18,20,21,23,24]. All three studies [2,20,23] that accounted for different confounding variables, such as age at onset and duration of T1DM, reported a significant inverse association between C-peptide and HbA1c levels. A meta-analysis was conducted in three cohort studies [13,17,38], and nineteen cross-sectional studies [2,4,5,7,8,13,15,20-29,31,44]. The pooled estimations of SMD indicated that HbA1c levels were lower in the detectable C-peptide group compared to the undetectable group, although this difference was not found to be statistically significant [pooled SMD (95% confidence interval (95% CI)): - 0.47 (- 1.05 to 0.10), I^2 = 97%, p.value: 0.11]. However, in subgroup analysis by study design, this difference reached statistical significance in the meta-analysis of the cohort studies [pooled SMD (95% CI): - 0.08 (- 0.13 to - 0.02), I^2 = 0%, p.value: 0.005] (Table 4, Figures 2 and 3a).



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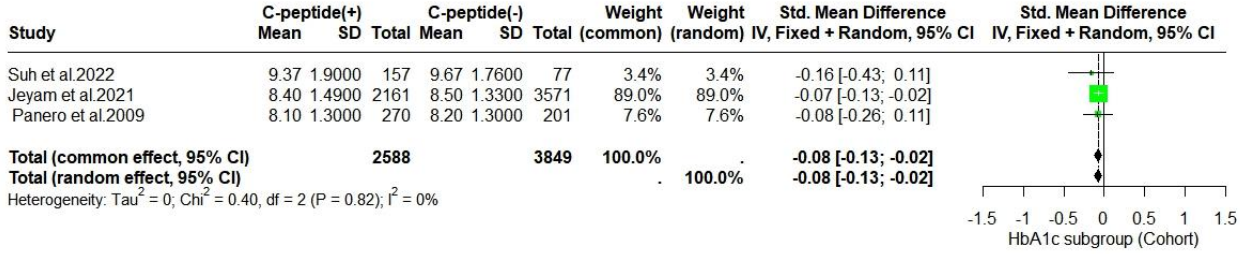

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Figure 2: Pooled estimations of standardized mean difference (SMD) and 95% confidence intervals (95% CIs) for HbA1c by study design: (a) Cross-sectional studies; (b) Cohort studies.
C-peptide (+) indicates the detectable C-peptide group, while **C-peptide (−)** indicates the undetectable C-peptide group. **SD** refers to standard deviations.
The **green squares** represent individual study estimates of the SMD, with their sizes reflecting the weight of each study in the meta-analysis. **Horizontal lines** depict the 95% CIs for each study's SMD, while the **diamonds at the bottom** represent the overall pooled estimates of the SMD along with its 95% CIs.

3.2. Daily Insulin Dose

The association between C-peptide and daily insulin dose was assessed by 20 studies, including 6 cohorts [14-18,21] and 14 cross-sectional studies [2,4,8,18,20,22,23,26-29,31,32,34], using different statistical approaches. Eleven [2,8,16-18,20,22,23,27,33] out of the twenty studies found a significant crude reverse association between C-peptide and daily insulin dose; Harsunen et al. [2] reported that the findings remained significant after adjusting for potential confounders, including age at onset, T1DM duration, BMI, and gender [β (95% CI): - 0.09 (- 0.11 to - 0.07)]

Overall, 13 studies [4,8,15,17,18,20,22,23,26,29,31,32,34] provided data on the size of mean differences for daily insulin dose between C-peptide groups, of which 7 studies [8,17,18,20,22,23,32] consistently found a significantly lower daily insulin dose in the detectable group. Based on our pooled analysis of SMD, there was a significant difference between detectable and undetectable C-peptide groups in this regard [pooled SMD (95% CI): - 0.41 (- 0.65 to - 0.18), I^2 = 83%, p.value < 0.001] (Table 4 and Figure 3b).

3.3. Hypoglycemia

The association between C-peptide and hypoglycemia, in terms of any occurrence of hypoglycemic events (any (n = seven studies [15,16,22,25,29,31,36]) or severe events (n = five studies) [7,15,20,35,37]) or percentage of time spent in the hypoglycemic range (n = four studies [8,14,21,26]), was evaluated by 15 studies; one study assessed both severe and any events of hypoglycemia [15].

Regarding hypoglycemic events (any and severe cases), seven studies [7,15,16,20,22,25,37] found significant findings, all suggesting that the detectable group experienced hypoglycemic events less frequently; however, only two studies [16,20] accounted for confounding factors. Sorensen et al. [20] found that individuals with T1DM in detectable C-peptide group significantly had lower odds for severe hypoglycemia after accounting for the confounding effect of T1DM duration, HbA1c level, and insulin dose [adjusted OR (95% CI): 0.4 (0.14 to 0.91)]. Jeyam et al. [16] conducted a cohort study showing that individuals with T1DM in detectable C-peptide group compared to others less frequently developed hypoglycemic events during a 5-year follow-up [Hazard ratio (HR) (95% CI): 0.35 (0.16 to 0.76)].

However, none of the four studies [8,14,21,26] performing glucose monitoring detected a significant difference in the percentage of time spent in the hypoglycemic range between the two study groups (Table 4).

3.4. DKA

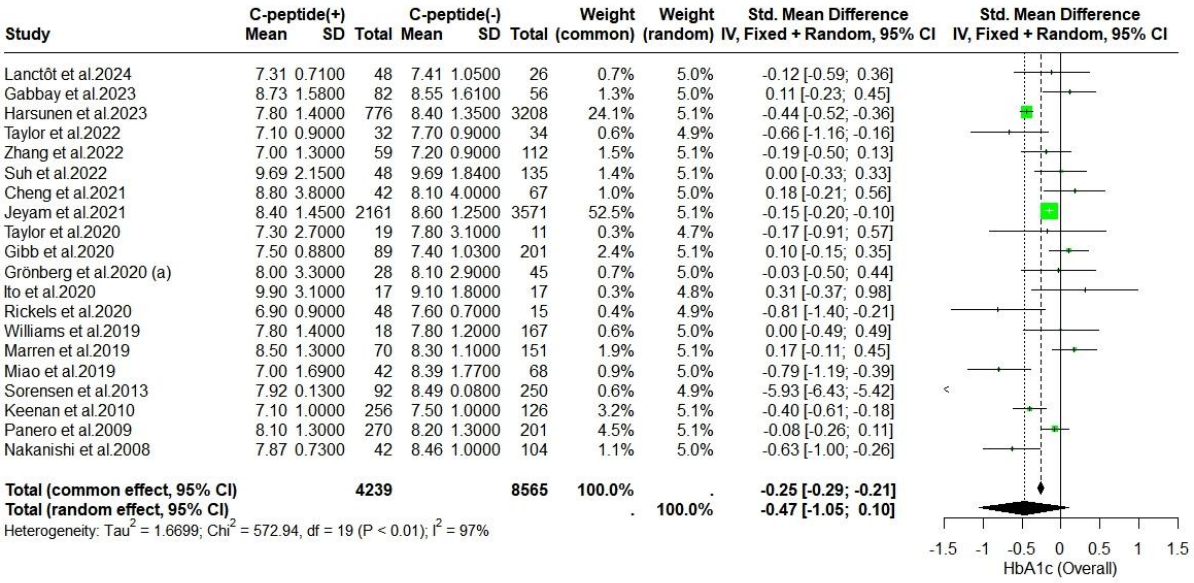
Three cohort studies, two retrospective cohort [17,38] (RC) and one prospective cohort [16] (PC), with mean follow-up duration of 5.2 to 15 years, compared the incidence of DKA events between individuals with T1DM in detectable and undetectable C-peptide groups. Lee et al.[38] and Jeyam et al. [16] studies found a lower risk of DKA in the detectable group; Jeyam et al. [16] considered confounding variables such as HbA1c, age at onset, sex, and T1DM duration (adjusted HR (95%

CI): 0.44 (0.29 to 0.67)). The RC study by Suh et al. [17] failed to detect a significant finding in this regard in their longitudinal analysis, but their cross-sectional analysis of data from the follow-up visit revealed that detectable C-peptide is associated with lower odds of DKA [crude OR (95% CI): 0.21 (0.06 to 0.74)].

3.5. Other glycemic control indicators

Most studies reported that C-peptide levels were directly associated with the percentage of time in the normoglycemic range (seven studies [8,14,18,21,28,32,39] out of eight studies [8,14,18,21,26,28,32,39]), and inversely associated with serum glucose levels (five studies [8,14,18,25,32] out of six studies [8,14,18,25,26,32]), glucose SD (two out of two studies [18,25]), CV (six studies [8,18,21,25,28,39] out of seven studies [8,18,21,25,26,28,39]), and MAGE (one out of one [18]) (Table 4).

Furthermore, four out of five studies [8,14,25,26,32] (one cohort [14] and three cross-sectional studies [8,25,32]) reported a significant inverse association between C-peptide levels and the percentage of time in the hyperglycemic range. However, none of them adjusted for potential confounding factors (Table 4).



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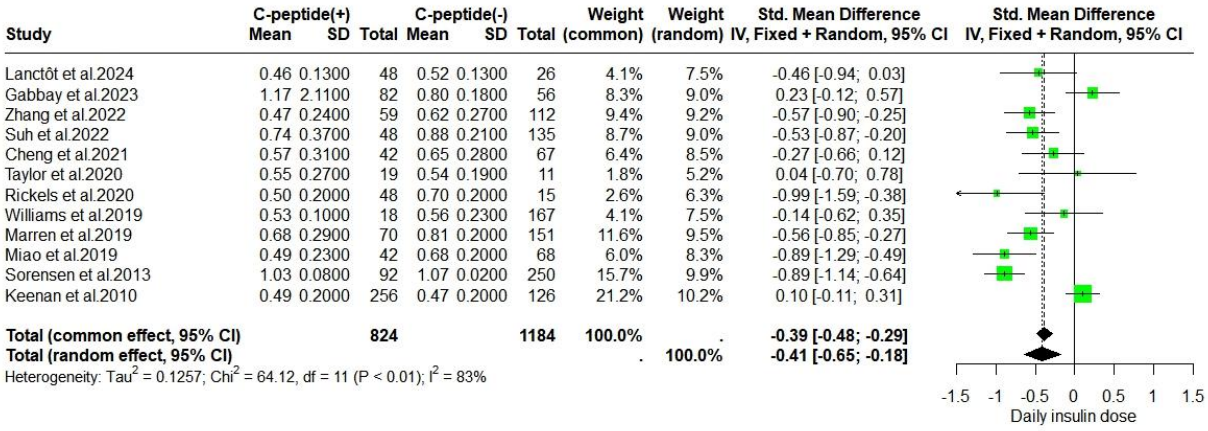

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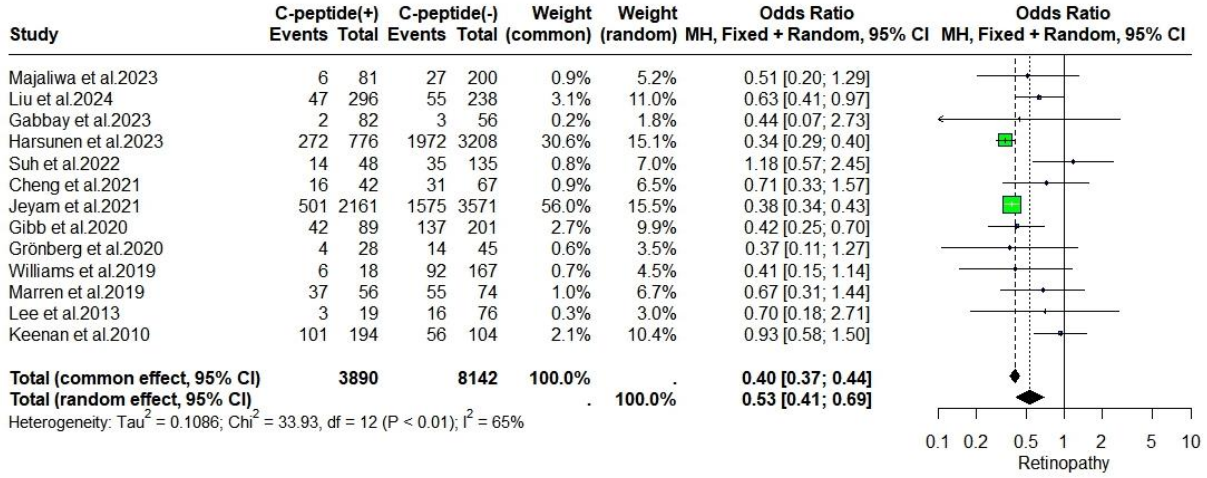

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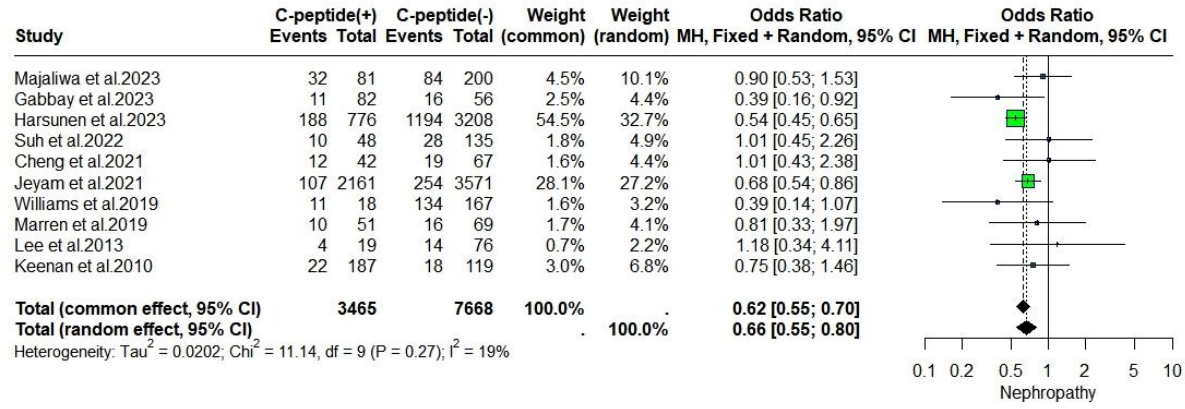

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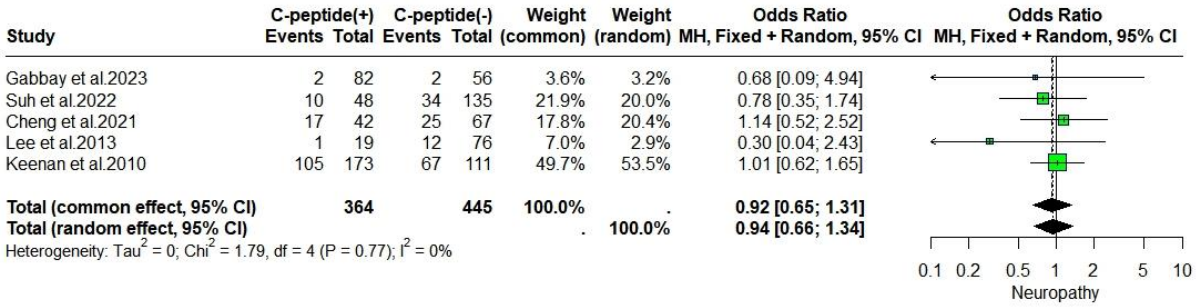

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Figure 3: Pooled estimations of standardized mean difference (SMD) or odds ratios (OR) with 95% confidence intervals (95% CIs) for: (a) HbA1c; (b) Insulin dose; (c) Retinopathy; (d) Nephropathy; and (e) Neuropathy.
C-peptide (+) indicates the detectable C-peptide group, while **C-peptide (−)** indicates the undetectable C-peptide group. **SD** refers to standard deviations.
The **green squares** represent individual study estimates of SMD or OR, with their sizes reflecting each study's weight in the meta-analysis. **Horizontal lines** show the 95% CIs for each estimate. The **diamonds at the bottom** represent the overall pooled estimates of SMD or OR and their 95% CIs.

3.6. Microvascular Complications

A total of 16 studies investigated the association between C-peptide status/levels and microvascular complications overall (n = 2) [7,13] or separately by its subtype, including retinopathy (n = 16) [2,4,5,12,15-17,22,25,29,30,34,38,40-42], nephropathy (n = 6) [2,15,17,29,30,40] and its related renal conditions (CKD stage 3 (n = 2) [16,34], albuminuria [micro (n = 5) [2,4,22,29,34], macro (n = 1) [34], micro or macro (n = 1) [38]], and renal failure (n = 1) [34] and/or neuropathy (n = 6) [4,15,17,29,34,38]).

Four [2,12,16,25] out of fifteen studies [2,4,5,12,15-17,22,25,29,30,34,38,40-42] on the association between C-peptide and retinopathy found a significant finding; two of them were the largest studies included in our review, conducted by Jeyam et al. [16] in 2021 (sample size = 5,732) and Harsunen et al. [2] in 2023 (sample size = 3,984), both of which adjusted for confounders. Based on our meta-analysis of both crude and adjusted OR, detectable C-peptide was significantly associated with lower odds of retinopathy in T1DM [pooled crude OR (95% CI): 0.53 (0.41 to 0.69), I^2 = 65%, p.value < 0.001], [pooled adjusted OR (95% CI): 0.70 (0.56 to 0.87)] (Table 4 and Figures 4 and 3c).

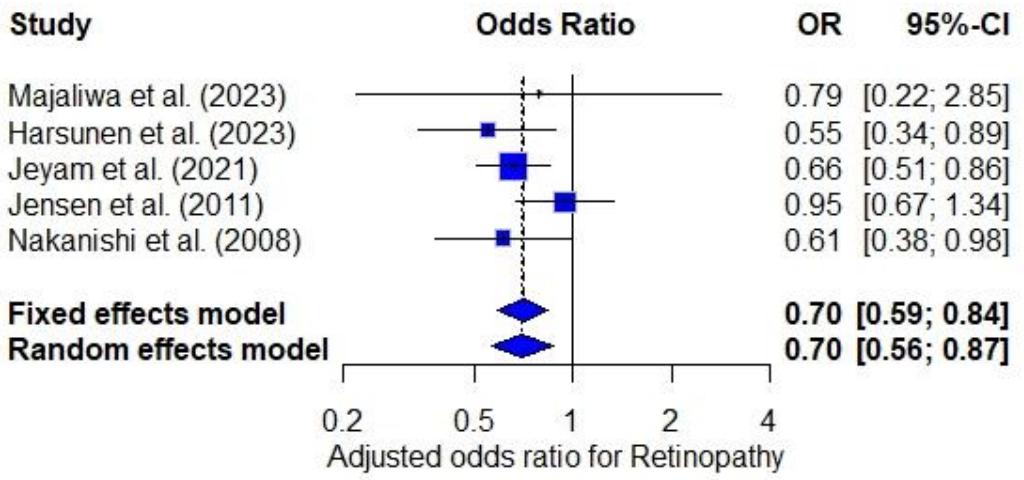

Figure 4: Pooled analysis of adjusted odds ratios (OR) and 95% confidence intervals (95% CIs) for retinopathy.
Each **blue square** represents the OR for an individual study, with the size reflecting the study's weight in the meta-analysis. **Horizontal lines** indicate the 95% CIs for each study's OR. The **diamonds at the bottom** represent the overall pooled estimates of the OR, along with their 95% CIs for both the fixed effects model and the random effects model.

A significant association between C-peptide levels and nephropathy was detected in two cross-sectional studies conducted by Gabbay et al. [29] [adjusted OR (95% CI): 0.4 (not reported)] and Harsunen et al. [2] [adjusted OR (95% CI): 0.61 (0.38 to 0.96)]. Regarding the association of C-peptide level with CKD stage 3 and renal failure, only Jeyam et al. [16] observed a significant OR in their cross-sectional analysis, suggesting the presence of a direct association [adjusted OR (95% CI): 1.95 (1.25 to 3.05)]; however, they failed to confirm this significant association in their longitudinal analysis. Of six studies [2,4,22,29,34,38] comparing the presence of albuminuria (microalbuminuria and/or macroalbuminuria) between study groups, a significantly lower odds of "microalbuminuria" in the detectable C-peptide group was reported by Gabbay et al. [29] [adjusted OR (95% CI): 0.39 (0.16 to 0.92)] and Harsunen et al. [2] [adjusted OR (95% CI): 0.71 (0.52 to 0.97)]; none of the four studies [4,22,34,38] reporting a non-significant association considered potential confounders (Table 4).

Our meta–analysis revealed that individuals with T1DM in the detectable C-peptide group had lower odds of nephropathy and its correlated renal conditions than those in the undetectable C-peptide group [pooled crude OR (95% CI): 0.62 (0.55 to 0.70), I2 = 19%, p.value < 0.001] (Figure 3d).

None of the six studies (two cohort [17,38] and four cross-sectional [4,15,29,34]) found a significant association between C-peptide levels and neuropathy complications [pooled crude OR (95%CI): 0.92 (0.65 to 1.31), I2 = 0%, p.value: 0.31] (Figure 3e).

3.7. Macrovascular complications

Five studies (including four cross-sectional studies [2,4,15,43] and one cohort study [13]) assessed the association between C-peptide levels and macrovascular complications. The cross-sectional study conducted by Harsunen et al. [2] found a significant association, revealing that individuals with T1DM in the detectable C-peptide group had a 40% lower risk of macrovascular complications [crude OR (95% CI): 0.60 (0.44 to 0.83)]. In contrast, Irilouzadian et al. [43] found that C-peptide levels were significantly associated with an increased risk of CAD among patients with T1DM [crude OR (95% CI): 1.62 (1.22 to 2.16)]. This association remained significant after adjusting for factors such as age, sex, BMI, diabetes duration, HbA1c, and fasting blood sugar [adjusted OR (95% CI): 1.65 (1.24 to 2.19)] (Table 4).

4. Discussion

This systematic review includes a total of 38 articles investigating the relationship between C-peptide status and critical parameters in individuals with T1DM. Individuals with T1DM in the detectable C-peptide group exhibited better glycemic control, as evidenced by their lower HbA1c levels and a reduced daily insulin requirement. Regarding microvascular complications, detectable C-peptide was associated with a lower risk of retinopathy and nephropathy; however, there was no association between detectable C-peptide levels and neuropathy.

Research indicates that T1DM can exhibit distinct progression patterns depending on the immunogenetic phenotypes of individuals with T1DM [45]. Young individuals with high immunogenetic risk tend to manifest the disease earlier in life and experience rapid progression toward absolute insulin deficiency [46]. However, some cases might maintain a level of insulin secretion throughout adulthood, potentially contributing positively to the course of the disease [47].

Pancreatic islet beta cells produce proinsulin, which is cleaved into insulin and C-peptide, both of which are released into the portal circulation in an equimolar ratio [48,49]. Unlike insulin, which is mostly eliminated during its first pass through the liver with a half-life of 3 to 10 minutes [50], C-peptide avoids initial metabolism and has a half-life of approximately 30 minutes, making it a

reliable indicator of beta cell function in clinical settings [51]. In individuals with T1DM, C-peptide levels are significantly decreased or nearly absent [52]. Decreases in these parameters indicate disease severity and increased reliance on exogenous insulin therapy for blood glucose management [53]. Additionally, a sudden increase in C-peptide levels has been associated with the remission phase of T1DM, a unique phase associated with the reduced risk of microvascular complications [54].

Although C-peptide has long been considered a by-product of insulin secretion, a growing body of evidence suggests that it has beneficial biological properties. These potential beneficial effects have been shown in animal and human kidney and mesangium cell lines. Further investigation is warranted to explore these impacts within human clinical environments. While the current focus of T1DM therapy revolves around the administration of external insulin, there is a hypothesis that the absence of simultaneous administration of C-peptide may result in a physiological gap and potentially play a role in the emergence of long-term complications associated with the disease [10].

Although there were some inconsistencies in the included studies regarding glycaemic control, our meta-analysis showed lower HbA1C and insulin doses in individuals with T1DM in the detectable C-peptide group. In addition, most studies have indicated that individuals in the detectable C-peptide group tend to have longer periods of normoglycemia. Remarkably, these advantages have been noted alongside a decrease in hypoglycemia occurrence. This result demonstrates that undetectable C-peptide levels can lead to increased reliance on external insulin, leading to the occurrence of both hyperglycemia and hypoglycemia. Consequently, more stringent disease management strategies are required for these individuals.

Our study showed that individuals with T1DM in the detectable C-peptide group experienced fewer microvascular complications. The longer periods of normoglycemia in these individuals result in a lower rate of non-enzymatic glycosylation, resulting in less endothelial damage and fewer microvascular complications [55]. Nevertheless, over the last decade, research has revealed that this hypothesis fails to account for all the advantageous impacts of C-peptide in this context [56]. Numerous studies have presented persuasive findings indicating that C-peptide's biological functionality can safeguard against microvascular leakage by obstructing vascular endothelial growth factor (VEGF)-induced microvascular permeability. This inhibition occurs through the suppression of reactive oxygen species (ROS)-mediated intracellular processes, preservation of

VE-cadherin integrity, and prevention of stress fiber formation [56]. However, most of the studies included did not adjust for diabetes duration, which may limit our understanding of C-peptide's role in glycemic control and the development of chronic complications in individuals with T1DM.

5. Conclusions

This study represents the first systematic review exploring the correlation between C-peptide levels and critical parameters in individuals with T1DM. Individuals who exhibit detectable C-peptide levels may experience enhanced control over their glycemic parameters, including reduced HbA1c levels, decreased daily insulin requirements, and decreased likelihood of DKA. Moreover, the presence of detectable C-peptide likely correlates with a lowered risk of hypoglycemic incidents. Detectable C-peptide is anticipated to reduce the risk of complications such as retinopathy, nephropathy, and related renal disorders. By addressing the physiological gap arising from insulin therapy regimens, C-peptide may open up novel avenues for enhancing the quality of life and long-term outcomes of individuals with T1DM. To comprehensively understand the direct effects of C-peptide, further investigations encompassing both basic and clinical studies are strongly encouraged.

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Table 1: Assessment of the included studies (cohort studies)

Author	Selection				Comparability	Outcome			Total Of 9 scores
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	4 The Outcome of Interest Was Not Present at Start of Study		Assessment of outcome	Enough follow-up to occur outcomes	Adequacy of follow up	
1. Nakanishi et al.	*	*	*	*	**	*	*	*	9
2. Panero et al.	*	*	*	*	**	*	*	*	9
3. Kristensen et al.	*	*	*	*	*	-	*	*	7
4. Jensen et al.	*	*	*	*	**	*	*	*	9
5. Lee et al.	*	*	*	*	*	*	*	*	8
6. Beato-Vıbora et al.	*	*	*	*	*	*	*	*	8
7. Henriksen et al.	*	*	*	*	**	*	*	*	9
8. Carr et al.	*	*	*	*	**	*	*	*	9
9. Jeyam et al.	*	*	*	*	**	*	*	*	9
10. Suh et al.	*	*	*	*	*	*	*	*	8
11. Zhang et al.	*	*	*	*	**	*	*	*	9
12. Grönberg et al[b].	*	*	*	*	*	*	*	*	9

Table 2: Assessment of the included studies (cross-sectional studies)

Author	Selection			Comparability	Outcome		Total score Of 7 scores
	Representativeness of the sample:	Non-respondents:	Ascertainment of the exposure (risk factor):		Assessment of the outcome:	Statistical test:	
1. Keenan et al.	*	*	*	*	*	*	6
2. Sorensen et al.	*	*	*	**	*	*	7
3. Rajalakshmi et al.	*	*	*	**	*	*	7
4. Kuhtreiber et al.	*	*	*	*	*	*	6
5. Buckingham et al.	*	*	*	*	*	*	6
6. Hwang et al	*	*	*	*	*	*	6
7. Marren et al.	*	*	*	*	*	*	6
8. Williams et al.	*	*	*	*	*	*	6
9. Miao et al.	*	*	*	**	*	*	7
10. Rickels et al.	*	*	*	*	*	*	6
11. Sugihara et al.	*	*	*	*	*	*	6
12. Gibb et al.	*	*	*	**	*	*	7
13. Gronberg et al[a].	*	*	*	**	*	*	7
14. Taylor et al[b].	*	*	*	**	*	*	7
15. Ito et al.	*	*	*	*	*	*	6
16. Cheng et al.	*	*	*	*	*	*	6
17. Wellens et al.	*	*	*	**	-	*	6
18. Babaya et al.	*	*	*	*	*	*	6
19. Taylor et al[a].	*	*	*	*	*	*	6

20. Gabbay et al.	*	*	*	*	*	*	6
21. Harsunen et al.	*	*	*	**	*	*	7
22. Majaliwa et al.	*	*	*	*	*	*	6
23. Irilouzadian et al.	*	*	*	*	*	*	6
24. Bhagadurshah et al.	*	*	*	*	*	*	6
25. Lanctôt et al.	*	*	*	**	*	*	7
26. Liu et al.	*	*	*	*	*	*	6

Table 3: Characteristic of the included studies

Author	Country	Study. Type	Inclusion criteria	Sample size			% Male (N)			Age at onset			Disease duration			Body mass index (Kg/m^2)		
				All	C-peptide		All	C-peptide		All	C-peptide		All	C-peptide		All	C-peptide	
					N	P		Ne	Po		Ne	Pos.		Neg	Pos		Ne	Po
1.Nakanishi et	Japan	RC	Outpatients/	254	104	42	57%	63%	52%	34.0	36 (1	30 (12)*	5 - 20	20	20	NR	NR	NR
2.Panero et al.	Italy	RC	Age <60	471	201	270	NR	55%	57%	NR	NR	NR	15.8 (10.	13.9 (9.1	7.8 (9.	NR	24.1	24.5
3.Kristensen et	Denmark	PC	Disease D. ≥	219	NR	NR	59%	NR	NR	25 (1	NR	NR	21 (12)	NR	NR	25 (3.6)	NR	NR
4.Jensen et al.	Sweden	PC	Dig. Age <	246	NR	NR	55%	NR	NR	24.9	NR	NR	NR	NR	NR	22.1 (3.7)	NR	NR
5.Lee et al. 2013	S.Korea	RC	Disease D.	95	76	19	41%	NR	NR	7.8 (4.	NR	NR	NR	NR	NR	0.23(1.05)	NR	NR
6.Beato-Vıbora	Spain	RC	Newly diagno	301	NR	NR	62%	NR	NR	27 (1	NR	NR	6.8 (4.5	NR	NR	NR	NR	NR
7.Henriksen et al.	Denmark	PC	Age >18	98	42	91	57%	NR	NR	NR	NR	NR	32 (11)	NR	NR	25 (4)	NR	NR
8.Carr et al. 2021	UK	PC	EXTOD	26	NR	NR	57%	NR	NR	27.2	NR	NR	New case	NR	NR	23.5 (3.1)	NR	NR
9.Jeyam et al.	UK	PC	SDRNT1BIO	5732	3571	2161	56%	54.7%	58.3%	20.8	17.0	25.9 (14.4)	20.9 (14.	25.4 (17.	11.7	26.3 (5.8)	26.4	26.2
10.Suh et al.	S.Korea	RC	Disease D. ≥	234	77	157	43%	NR	NR	8.3	NR	NR	NR	NR	NR	0.25 (1.15)	NR	NR
11.Zhang et al.	China	RC/C	Disease D. ≥	171	112	59	43%	43%	42%	NR	NR	NR	1.6 (1.9	2.0 (2)	0.7 (0.	18.6 (3.4)	18.7	18.5
12.Gronberg et	Sweden	PC/C	Newly diagno	50	30	20	44%	50%	35%	10.6	11.1	10.0 (2.3)	NR	NR	NR	−0.07 (1.26)	0.08	−0.29
13.Keenan et al.	US	CS	Disease D. ≥	382	126	256	48.4%	42.6	51%	11 (6.	10.9	11.1 (6.2)*	56.2 (5.8	56.4 (5.7	56.0	26.0 (5.1)	26.7	25.9
14.Sorensen et al.	Denmark	CS	Dig. Age <	342	250	92	51%	51%	49%	9.2 (3.	8.4 (3.	9.0 (2.6)*	4.2 (0.9	4.4 (0.9	3.9 (0.	NA	NA	NA
15.Rajalakshmi	India	CS	Dig. Age <	150	NR	NR	56%	NR	NR	16.8	NR	NR	12.4 (7.4	NR	NR	22.1 (3.6)	NR	NR
16.Kuhtreiber et al. 2015	US/Ca	CS	-	1272	NR	NR	43%	NR	NR	20.6 (1	NR	NR	19 (14.8)	NR	NR	NR	NR	NR
17.Buckingham	US	CS ‡	Newly diagno	67	NR	NR	NR	NR	NR	NR	NR	NR	New case	NR	NR	NR	NR	NR
18.Hwang et al 2017	Korea	CS	Newly diagno	34	27	7	44%	11%	33%	10 (4.6)	9 (4.3)	13.6 (3.6)*	3 (NR)	3 (NR)	3 (NR)	16.1 (2.8)	15.5 (3	18.7 (3
19.Marren et al. 2019	UK	CS	Dig. Age < 20	221	151	70	52%	57%	41%*	8.9 (8.2)	6.1 (7.9)	15.1 (7.2)*	13.0 (11.4)	13.3 (11.9)	12.6 (10	23.9 (4.2)	23.3 (4	25.2 (3
20.Williams et	US	CS	Dig. Age <	185	167	18	49%	49%	50%	<17	8.1 (4.	9.7 (4.2)	42.9 (6.7	43.0 (6.7	42.1	28.2 (5.1)	28.4	26.7
21.Miao et al. 2019	China	CS	C-peptid o >	110	68	42	43%	36%	55%*	20.6 (5	19.2 (5	22.8 (5.9)	2.5 (1.8	2.3 (1.7	2.7 (1.7)	19.4 (4.4)	19.1 (5	19.8 (3
22.Rickels et al.	US	CS	Age 18 to	63	15	48	46%	53%	52%	NR	NR	NR	7.4 (6.3	13 (9)	5.6 (3.	24.2 (2.9)	25 (3)	24 (3)
23.Sugihara et al.	Japan	CS	Dig. Age <	576	NR	NR	40%	NR	NR	5	NR	NR	1.1	NR	NR	NR	NR	NR
24.Gibb et al.	UK	CS	Disease D. ≥	290	201	89	56%	54%	60%	17.4	15 (1	23 (10.3)	21.9 (13.	25 (14.	15 (11	26.7 (4.6)	26.6	27.2
25.Gronberg et	Sweden	CS	Age < 25	73	45	28	55%	64%	39%*	5.1 (3.	5.0 (2.	5.2 (3.1)	12.3 (2.4	12.7 (2.6	11.8	0.52 (1.06)	0.28	0.90

26.Taylor et al[b].	UK	CS	Disease D. ≥	30	11	19	53 %	45 %	58 %	18.2	13.27	21 (9.2)*	19.9 (13.	26.8 (13.	16.0	25.2 (3.7)	25.6	24.9
27.Ito et al. 2020	Japan	CS	Age >16	34	17	17	47 %	47 %	59 %	NR	NR	NR	8.1 (9.1	11.1 (9.2	5.1 (8.	22.5 (4.5)	22.5	22.6
28.Cheng et al.	China	CS	Disease D.	109	67	42	40 %	45 %	33 %	19.0	17.0	27.5(25.5)	13 (3.7	13.0 (3.7	12.0	20.6 (2.5)	20.6	20.7
29.Wellens et al.	Netherlands	CS	Disease D. ≥	509	NR	NR	41 %	NR	NR	12 (8.	NR	NR	19 (13.	NR	NR	25.0 (3.59)	NR	NR
30.Babaya et al.	Japan	CS	Non pregna	19	NR	NR	32 %	NR	NR	NR	NR	NR	8.8 (9.6	NR	NR	21.7 (3.8)	NR	NR
31.Taylor et al[a].	UK	CS	Disease D ≥	66	34	32	56 %	53 %	53 %	20 (1	18 (1	22 (12.5)	21.5 (12.	25 (11)	17.9	25.4 (3.3)	25.4	25.5
32.Gabbay et al.	Brazil	CS	Disease D. ≥	138	56	82	59 %	57 %	60 %	9.0 (0.	8.7 (5.	10.2 (5.6)*	12.0 (0.5	14.7 (6.7	11.4	23.0 (0.3)	23.1	23.5
33.Harsunen et	Finland	CS	FinnDiane	3984	3208	776	51 %	50 %	55 %	13·5	12·6	18.6 (9.8)*	21·6 (13.	23·3 (12.	12.1	24.7 (3.7)	24.8	24.4
34.Majaliwa et	Tanzania	CS	Age: 0 to 20	281	200	81	49 %	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
35.Irilouzadian et	Iran	CS	Disease D. ≥	279	NR	NR	50 %	NR	NR	NR	NR	NR	43.4 (4.1	NR	NR	26.5 (4.7)	NR	NR
36.Bhagadurshah	India	CS	Disease D. ≥	113	NR	NR	55 %	NR	NR	15 (3.	NR	NR	16 (6.7	NR	NR	22.04 (3.9)	NR	NR
37.Lancôt et al.	Canada	CS	Disease D. >	74	26	48	55 %	58 %	54 %	NR	10 (6.	10 (8.1)	54 (4.4	54 (3.7	54 (4.	NR	26.5	26.7
38.Liu et al. 2024	China	CS	fCP >1,500	534	238	296	46 %	42 %	49 %	36 (2	30 (2	38 (20.0)	9.0 (13.	15.0	4.0 (8.	22.8 (3.3)	23.1	22.

ACEIs: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers; BS: Blood sugar; Ca: Canada; CS: Cross-sectional; DISS: Diabetes Incidence Study in Sweden; Dig. Age: Diagnosis age; Disease D.: Disease Duration; S.Korea: South Korea; EDC: Pittsburgh Epidemiology of Diabetes Complications; FinnDiane: The Finnish Diabetic Nephropathy; EXTOD: Exercise in Type 1 Diabetes; JSGIT: The Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes; Neg.: Negative (Undetectable group); NR: Not reported; PC: prospective cohort; Pos.: Positive (Detectable group); RC: Retrospective cohort; SDRNT1BIO: The Scottish Diabetes Research Network Type 1 Bioresource; * P Value <0.05, † SDS, ‡ Panel study

Table 4: Association of detectable C-peptide levels with glycemic control and chronic complications in patients with Type 1 Diabetes mellitus

Id	Author	Type study	C-peptide method	C-peptide test	FU D.	Cut-P. IV Pmol/L	Outcomes	Sign.	Direction	Effect size for C-peptide (95% CI) [Detectable vs. Undetectable]	Confounders
1	Nakanishi et al.	RC	RIA	fCP/PCP	5-20	fCP > 17 or PCP> 33	HbA1c at 5 & 10 Yrs. Follow up HbA1c at 15 Yrs. Follow up HbA1c at 20 Yrs. Follow up Retinopathy at Yrs. Follow up Retinopathy at 10 Yrs. Follow up Retinopathy at 15 Yrs. Follow up Retinopathy at 20 Yrs. Follow up	NS + + NS + + +	NA ↓ ↓ NA ↓ ↓ ↓	- MD= -0.44 (-0.76 to -0.12) MD= -0.59 (-0.93 to -0.25) - HR= 0.70 (0.53 to 0.93) HR= 0.65 (0.48 to 0.88) HR= 0.61 (0.37 to 0.96)	None // // Sex, HTN, HbA1c, time to insulin therapy, age at onset // // //
2	Panero et al.	RC	NR	fCP	4.5	60	HbA1c at baseline Microvascular complications Macrovascular complications	NS + NS	NA ↓ NA	- OR= 0.59 (0.37 to 0.94) -	None Age, sex, Duration of diabetes, HbA1c, CVD, and HTN //
3	Kristensen et al.	PC	RIA	rCP	1	10	Severe hypoglycemia	NS	NA	-	None
4	Jensen et al.	PC	NR	NR	15	130	Retinopathy	NS	NA	-	HbA1c, HTN, HLA and islet autoantibodies
5	Lee et al.	RC	RIA	fCP	15	50	Retinopathy Peripheral Neuropathy Albuminuria	NS NS NS +	NA NA NA ↓	- - - Risk Diff. = 26.3 %	None // // //

							History of DKA			(1.5% to 43%)	
6	Beato-Vıbora et al	RC	CLIA	fCP /GST	6(4.8)	NR	Insulin dose	+	↓	P value <0.05	None
7	Henriksen et al.	PC	NR	NR	12	10	Hypoglycemia	NS	NA	-	None
8	Carr et al.	PC	NR	MMTT	1	100	HbA1c Inulin dose % Time in normoglycemia glucose SD % Time in hyperglycemia % Time in hypoglycemia	NS NS + + + NS	NA NA ↑ ↓ ↓ NA	- - β = 2.39% (0.51-4.26) β = -0.14(-0.25 to -0.023) β = -2.64 (–4.87 to –0.41) -	None // // // // //
9	Jeyam et al.	PC	ECLIA	rCP	5.2	> 200 vs. < 5	HbA1c at Baseline HbA1c at Fu. Insulin dose DKA during Fu. Hypoglycemia during Fu. Retinopathy at Baseline Retinopathy at Fu. CKD Stage 3 at Baseline CKD at Fu.	+ + + + + + + + NS	↓ ↓ ↓ ↓ ↓ ↓ ↑ NA	β= -6.41, (-7.9 to -4.9) β= -4.90 (-6.2 to -3.6) β= -0.04 (-0.0 to -0.03) HR= 0.44 (0.29 to 0.67) HR= 0.35 (0.16 to 0.76) OR= 0.66 (0.51 to 0.86) OR= 0.51 (0.35 to 0.74) OR= 1.95 (1.25 to 3.05) -	None // // HbA1c, Age at onset, Sex, and Duration of diabetes // // // // //
10	Suh et al.	RC	RIA	PCP	15	500	HbA1c Insulin dose Insulin dose [CS Analysis] DKA	NS + + NS +	NA ↓ ↓ NA ↓	- MD= -0.14 (-0.22 to -0.07)	None // // // //

							DKA [CS Analysis] Retinopathy Neuropathy Nephropathy	NS NS NS	NA NA NA	MD= -0.14 (-0.23 to -0.05) - OR= 0.21 (0.06 to 0.74) - - -	// // //
11	Zhang et al.	RC	CLIA	MMTT	0.5	200	HbA1c at baseline HbA1c changes in 6 months % Time normoglycemia mean glucose glucose SD MAGE Glucose CV Insulin dose at baseline	NS + + + + + + +	NA ↓ ↑ ↓ ↓ ↓ ↓ ↓	- P value <0.05 R= + 0.359 R= - 0.218 R= - 0.418 R= - 0.393 R= - 0.435 MD= -0.15 (-0.23 to -0.07)	None // // // // // // //
12	Gronberg et al[b].	PC	FIA	MMTT	6	30	HbA1c at diagnosis and FU. visits Insulin dose at diagnosis and FU. visits	NS NS	NA NA	- -	None //
13	Keenan et al.	CS	RIA	MMTT	NA	30	HbA1c Insulin dose Retinopathy Microalbuminuria Neuropathy CVD	+ NS NS NS NS NS	↓ NA NA NA NA NA	MD: -0.40 (-0.61 to -0.19) - - - - -	None // // // //
14	Sorensen et al.	CS	FIA	MMTT	NA	40	HbA1c [C-peptide :>200 vs. < 40] HbA1c [C-peptide :>40-200 vs. < 40]	+ + + +	↓ ↓ ↓ ↓	Diff in % = -12.9% (-17.9 to -7.5) Diff in % = -5.3% (-9.1 to-1.3)	Sex, age, pubertal status, Duration of diabetes, insulin admin technique

							Insulin dose [C-peptide :>200 vs. < 40] Severe hypoglycemia			Diff in % = -21.1% (-30.5 to -10.4) OR= 0.4 (0.14 to 0.91)	// // // & HbA1c level, and insulin dose
15	Rajalakshmi et al.	CS	EL	fCP /PCP	NA	NR	Retinopathy	NS	NA	-	None
16	Kuhtreiber et al.	CS	ELISA	fCP	NA	10	HbA1c Severe hypoglycemia Microvascular complications	+ + +	↓ ↓ ↓	P value < 0.05 // //	None // //
17	Buckingham et al.	CS‡	NR	MMTT	2	NA	HbA1c % Time in normoglycemia Glucose CV % Time in hypoglycemia	+ + + NS	↓ ↑ ↓ NA	P value < 0.05 β= 0.53 (0.23 to 0.83) β= -1.19 (-1.69 to -0.69) -	None // // //
18	Hwang et al	CS	IA	fCP	NA	198	HbA1c	NS	NA	-	None
19	Marren et al.	CS	CLIA	MMTT	NA	20	HbA1c Hypoglycemia Insulin dose Retinopathy Microalbuminuria	NS + + NS NS	NA ↓ ↓ NA NA	- HR = 0.79 (NR) MD= -0.13 (-0.20 to -0.06) - -	None // // // //
20	Williams et al.	CS	ELISA	fCP	NA	1.15	Insulin dose Retinopathy Microalbuminuria Macroalbuminuria CKD stage 3 Renal failureDS Polyneuropathy	NS NS NS NS NS NS	NA NA NA NA NA NA	- - - - - -	None // // // // //

21	Miao et al.	CS	IA	OGTT	NA	600	HbA1c Insulin dose Mean HbA1c during proceeding years (median 32.5 months)	+ + +	↓ ↓ ↓	MD= -1.39 (-2.07 to -0.71) MD= -0.19 (-0.27 to -0.11) OR= 0.41 (0.24 to 0.68)	None // HLA, age at onset, sex, family history of T1DM, DKA, BMI
22	Rickels et al.	CS	NR	MMTT	NA	0.007	HbA1c Insulin dose Mean glucose % Time in normoglycemia % Time in hyperglycemia Glucose CV % Time in hypoglycemia	NS + + + + NS	NA ↓ ↓ ↑ ↓ ↓ NA	- MD= -0.20 (-0.32 to -0.08) R = –0.356 r = +0.456 r = –0.376 r = –0.258 -	None // // // // // //
23	Sugihara et al.	CS	ECLIA	rCP	NA	NR	HbA1c	+	↓	R = –0.16	None
24	Gibb et al.	CS	IA	rCP	NA	10	HbA1c Retinopathy Glucose SD > 4.0 mmol/l Glucose CV > 40.3% [med] Interquartile range glucose > 5.6 mmol/l [med] Hypoglycemia > 9 times / 2 Weeks [med] % Time in hyperglycemia > 4% [med]	NS + + + + + +	NA ↓ ↓ ↓ ↓ ↓ ↓	- OR= 0.42 (0.25 to 0.70) OR= 0.32 (0.16to0.63) OR= 0.30 (0.17 to 0.52) OR= 0.40 (0.21–0.75) OR= 0.29 (0.15–0.54) OR= 0.32 (0.17–0.60)	None // // // // // //
25	Gronberg et al[a].	CS	ELISA	rCP	NA	1.17	HbA1c Retinopathy	NS NS	NA NA	- -	None //
26	Taylor et al[b].	CS	ECLIA	MMTT	NA	3	HbA1c Insulin dose Mean glucose	NS NS NS	NA NA NA	- - -	None // //

							% Time in normoglycemia % Time in hyperglycemia Glucose CV % Time in hypoglycemia	NS NS NS NS	NA NA NA NA	- - - -	// // // //
27	Ito et al.	CS	ECLusys	MMTT	NA	100	HbA1c Insulin dose	NS +	NA ↓	- MD= -17.3 (-28.8 to -5.8)	None //
28	Cheng et al.	CS	CLIA	fCP/PCP	NA	16.7	HbA1c Hypoglycemia Severe hypoglycemia Insulin dose Retinopathy Proliferative retinopathy Nephropathy Sever nephropathy peripheral neuropathy macrovascular complications	+ + NS NS NS NS NS NS NS NS	↓ ↓ NA NA NA NA NA NA NA NA	MD= -7.80 (-15.29 to -0.31) OR= 0.29 (0.12 to 0.67) - - - - - - -	None // // // // // // // //
29	Wellens et al.	CS	IRMA	fCP	NA	3.8	Impaired awareness of hypoglycemia Severe hypoglycemia (self-reported)	+ +	↓ ↓	OR= 0.51 (0.26 to 0.98) OR= 0.64 (0.38 to 1.08)	Age at onset, BMI, and T1DM complications None
30	Babaya et al.	CS	NR	fCP	NA	NR	Glucose CV	+	↓	R= - 0.64	None
31	Taylor et al[a].	CS	NR	UCPCR	NA	> 200 vs. < 1	HbA1c Insulin dose % Time in Nocturnal normoglycemia % Time in PP normoglycemia	NS NS + + +	NA NA ↑ ↑ ↓	- - MD= 18.00 (6.50 to 29.50) MD= 17.00 (4.35 to 29.65)	None // // // //

							Nocturnal CV (mmol/L)			MD= -0.40 (-0.63 to -0.16)	
32	Gabbay et al.	CS	ELISA	fCP	NA	1.15	HbA1c Insulin dose Hypoglycemia Nephropathy Microalbuminuria Neuropathy Retinopathy	NS NS NS + + NS NS	NA NA NA ↓ ↓ NA NA	- - - OR= 0.4 (NR) OR= 0.39 (0.16 to 0.92) - -	None // // Diabetes duration and HbA1c. // None //
33	Harsunen et al.	CS	UIA	rCP	NA	≥ 20	HbA1c Insulin dose Nephropathy microalbuminuria Retinopathy Hard CVD events	+ + + + + +	↓ ↓ ↓ ↓ ↓ ↓	β= - 4·97 (-6·28 to -3·67) β= - 0.09(-0.11 to -0.07) OR= 0·61 (0·38 to 0·96) OR= 0·71 (0·52 to 0·97) OR= 0·55 (0·34 to 0·89) OR= 0.60 (0.44 to 0.83)	Age at onset, sex, duration of diabetes, and BMI // // & HbA1c and its variability, hypertension, smoking, and eGFR // // None
34	Majaliwa et al.	CS	ELISA	fCP	NA	200	HbA1c Nephropathy Retinopathy	NS NS NS	NA NA NA	- - -	None // //
35	Irilouzadian et al.	CS	CIA	UCPCR	NA	NR	Coronary artery disease	+	↓	OR= 1.54 (1.16 to 2.05)	Adjusted for age, sex, BMI, diabetes duration, HbA1c, FBS, active smoking, alcohol consumption, HTN, Lipid profile, eGFR, uric acid, albumin, creatinine

											and albuminuria.
36	Bhagadurshah et al.	CS	ECLIA	rCP	NA	NR	Retinopathy Nephropathy	NS NS	NA NA	- -	None //
37	Lanctôt et al.	CS	IA	fCP	NA	33	HbA1cInsulin dose Hypoglycemic events in past month (per week)	NS NS NS	NA NANA	- - -	None // //
38	Liu et al.	CS	ECLIA	fCP/MMTT	NA	10	Diabetic retinopathy Insulin dose HbA1c > 7% eGFR % Time in normoglycemia Mean glucose % Time in hyperglycemia	+ + NS NS + + +	↓ ↓ NA NA ↑ ↓ ↓	OR= 0.63 (0.41 to 0.97) OR= 1.04 (1.02 to 1.06) - - Diff in % = 12.1 (3.64 to 20.35)MD = 1.50 (1.08 to 1.92) Diff in % = 17.0 (8.83 to 24.94)	None // // // // // //

BMI: Body mass index; CLIA: chemiluminescence immunoassay; CLEIA: Electrochemiluminescence immunoassay; CS: Cross-sectional; CV: coefficient of variation; CVD: Cardiovascular disease; Diff in %: percentage difference; DS Polyneuropathy: Distal symmetric polyneuropathy; DKA: Diabetic ketoacidosis; ECLIA: Electrochemiluminescence immunoassay; eGFR: estimated glomerular filtration rate; FBS: Fasting blood sugar; fCP: Fasting C-peptide; Fu.: Follow up; GST: Glucagon stimulation test; HLA: human leukocyte antigens; HR: Hazard ratio; HTN: Hypertension; IA: Immunoassay; MAGE: mean amplitude of glucose excursions; MD: Mean difference; Med: Median; MMTT: mixed meal tolerance test; NA: Not applicable; OR: Odds ratio; PC: Prospective cohort; PCP: Postprandial C-peptide; PP: Postprandial; RC: Retrospective cohort; RR: Relative ratio; rCP: Random C-peptide; RIA: Radioimmunoassay; SD: Standard deviation.

Highlights

- We have summarized the available evidence on the clinical significance of detectable levels of C-peptide in T1DM.
- A systematic search and meta-analysis were performed using online databases.
- Individuals with T1DM in the detectable C-peptide group, compared with the undetectable C-peptide group, had lower mean HbA1c (- 0.08) and daily insulin dose (- 0.41) and showed lower odds for retinopathy (pooled crude odds ratios: 0.53) and nephropathy complications (0.62).
- Individuals with T1DM in the detectable C-peptide group may experience better clinical outcomes.