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Original Research

The Predictive Potential of C-Peptide in Differentiating Type 1 Diabetes From Type 2 Diabetes in an Outpatient Population in Abu Dhabi

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ABSTRACT

Purpose: We aimed to investigate the predictive potential of plasma connecting peptide (C-peptide) in differentiating type 1 diabetes (T1D) from type 2 diabetes (T2D) and to inform evidence-based diabetes classification criteria.

Methods: A retrospective review was performed of all the patients with diabetes visiting an outpatient diabetology, endocrinology, general practice and family medicine tertiary health care center between January 2016 and December 2021.

Findings: Two hundred twelve individuals with diabetes were included, 85 (44.8%) with T1D and 127 (55.2%) with T2D. Mean (SD) age at diagnosis was 35.9 (15.1) years, and 112 (52.8%) men. Median (interquartile range [IQR]) duration of diabetes was 3.8 (3.0–4.5) years (T1D, 3.9 [3.5–4.6]; T2D, 3.4 [2.4–4.4]; $P = 0.001$). Body mass index was <18.5 kg/m^2 in 5 (2.5%) individuals (T1D, 5; T2D, none), 18.5 to <25 kg/m^2 in 57 (28.5%) (T1D, 32; T2D, 25), 25 to <30 kg/m^2 in 58 (29%) (T1D, 28; T2D, 30), and >30 kg/m^2 in 80 (40.0%) (T1D, 20; T2D, 60). Median (IQR) glycosylated hemoglobin was 7.4% (6.7%–8.5%) (T1D, 8.3% [7.2%–9.9%]; T2D, 7% [6.3%–7.6%]; $P = 0.0001$). Median (IQR) C-peptide concentration was 0.59 nmol/L (0.01–1.14 nmol/L) (T1D, 0.01 nmol/L [0.003–0.05 nmol/L]; T2D, 1.03 nmol/L [0.70–1.44 nmol/L]; $P = 0.0001$). C-peptide concentration of ≤0.16 nmol/L showed 92.9% sensitivity, 1-specificity of 2.4%, and AUC of 97.2% (CI, 94.7%–99.6%; $P = 0.0001$) in differentiating T1D from T2D.

Implications: To our knowledge, this is the first study in the Middle East and North Africa region highlighting the role of C-peptide in diabetes classification. The estimated cutoff point for C-peptide concentration (≤0.16 nmol/L) will certainly help in accurately classifying the T1D and will rule out the routine clinical judgmental approaches in the region, especially in those scenarios and periods where it is always difficult to diagnose the diabetes type. Quantifying the cutoff for C-peptide is among the vital strengths of this study that will provide a better treatment plan in diabetes care management. Also, we evaluated concomitant glucose levels to rule out the phenomenon of falsely low C-peptide values in the setting of hypoglycemia or severe glucose toxicity. Based on our findings, C-peptide testing could be included in postulating an evidence-based guideline that differentiates T1D from T2D. Despite this, our study has some limitations, including the selection bias due to the retrospective design and low C-peptide levels could be indicative of low pancreatic reserves due to other causes or long-standing T2D, and quantifying these reasons requires additional resources and time.

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Introduction

Diabetes mellitus (DM) is a serious health issue in developed countries and has now become a global concern because of its increasing prevalence.[1–4] This makes it one of the most significant concerns and threats when it comes to community health in the 21st century.[5,6] According to the latest International Diabetes Federation data published in year 2021, almost 537 million people were living with DM worldwide, and the number will increase to 634 million by 2030.[7] Nearly 73 million cases with diabetes were reported in the Middle East and North Africa (MENA) region in 2021, making DM the biggest issue in this region, with the United Arab Emirates (UAE) being particularly afflicted. The UAE has one of the fastest-growing adult diabetes prevalence in MENA, with more than 2 million adults expected to be diagnosed with diabetes by 2040. With diabetes being so prevalent in the country, effective prevention and management techniques must be developed to decrease its impact on people and society as a whole.[8]

Historians have long recognized 2 major forms of DM, namely, type 1 diabetes (T1D) and type 2 diabetes (T2D). Diabetes categorization, as well as diagnosis criteria and procedures, have evolved over the years.[9,10] T1D, also known as juvenile diabetes, is described as an autoimmune or idiopathic death of cells that leads to severe insulin insufficiency, as opposed to T2D, which is distinguished by insulin resistance.[11–13] Furthermore, T1D has long been seen as a disorder that mostly affects children and adolescents (aged 10–19 years),[14] and as a result, diagnosis, clinical management, and advocacy have usually focused on younger populations.[15] However, recent epidemiologic studies and the development of the T1D index—a data simulation tool that estimates the number of cases with T1D for all ages across countries—have revealed that adults account for the vast majority of T1D incidence and prevalence.[16,17] It is believed that up to 40% of persons aged >30 years with T1D were misdiagnosed as having T2D.[18] One of the most likely contributing factors to misdiagnosis is that certain people with T1D may not require insulin at the time of diagnosis (eg, persons with adult latent autoimmune diabetes), causing their clinical disease to be mislabeled as T2D.[19,20] Furthermore, some risk factors for T2D, such as obesity and metabolic syndrome, are now much more common in the general population and cannot be used to rule out a diagnosis of T1D.[21] Traditionally, T2D was considered an adult-onset disease, and T1D was typically diagnosed in children and young adults. However, the rise in obesity and sedentary lifestyles has led to an increase in T2D among younger populations. This shift can lead to diagnostic challenges because health care providers may assume that a young patient with diabetes has T1D rather than T2D. Moreover, both T1D and T2D can present with hyperglycemia and similar symptoms such as increased thirst, frequent urination, and unexplained weight loss. This overlap can complicate accurate diagnosis. Furthermore, If T2D is confirmed, the use of SGLT2 inhibitor and GLP-1 receptor agonists, with proven records in randomized clinical trial's evidences and in guidelines, has shown significant reduction in major adverse cardiovascular events, heart failure, chronic kidney disease progression, and lower extremity imputation (GLP-1 receptors agonist) with significant impact on mortality and morbidity.[22,23] These agents are not used in T1D and therefore establishing a precise diagnosis is clinically relevant. In the Steno-2 study, the intensive glycemic control in patients with T2D coupled with multiple risk factors' modifications resulted in significant increase in life expectancy by almost 13 years.[24] From a clinical standpoint, the misclassification of a patient with true T2D as having T1D will have major consequences in terms of treatment. This patient will only receive insulin and will be deprived of important modern life-saving therapies such as SGLT2 inhibitors and GLP-1, which will lead to increased cardiorenal risk in addition to the weight gain caused by insulin, which is in fact reversed with GLP-1 receptor agonist. In other words, the treatment algorithm will be completely different if connecting peptide (C-peptide) confirms the presence of T2D rather than T1D. The prevalence of T2D in general population is far greater than that of T1D; however, the misclassification of younger patients in T1D when they indeed have onset of T2D will have a great impact on their life expectancy. In addition, both T1D and T2D have a great impact on survival and lifetime risk of cardiovascular events in patients than in the general population.[25,26] Most recently, increased diagnosis of T1D was reported in Europe and United States with up to 4% annual increase.[27] Given this observation, it has become critically important to truly differentiate between T2D and T1D with a precise biomarker because the assigned treatment and subsequent reduction in event rate will be vastly different over the patient's lifespan, which is particularly important in younger patients considering the legacy affect and cumulative exposure over decades. Given that people with T1D have a life expectancy that is up to 8 years less than that of the general population, compared with 3 years for T2D, a paradigm shift toward greater awareness and accuracy in the diagnosis of T1D in adults is required in the clinical and research fields.[17,28]

According to the American Diabetes Association guidelines,[29] T1D screening is usually based on the presence of autoantibodies to insulin, such as auto-islet antigen-2, glutamic acid decarboxylase (GAD), or zinc transport 8, in addition to overt hyperglycemia, which is often difficult to perform. It is also crucial to note that the diagnostic algorithm for T1D is not as simple as that for T2D, making categorization even more complex. Testing the C-peptide levels in the blood is a more prompt and cost-effective method that might help in predicting and differentiating T1D from T2D. A substantial correlation between plasma C-peptide levels and diabetes has already been documented in the literature.[30,31] Examining C-peptide levels could be an essential component in differentiating between and identifying the 2 types of diabetes because it indicates how much insulin is naturally produced.[31–33] However, the goal of this investigation is to determine whether plasma C-peptide could be used to predict and differentiate T1D from T2D.

Material and Methods

Participants and Study Design

This study follows an observational retrospective cohort design and was conducted at Burjeel Hospital, Abu Dhabi, UAE. This center is the most comprehensive private tertiary health care provider operating specialist clinics in diabetology, endocrinology, cardiology, oncology, nephrology, orthopedics, ophthalmology, urology, neurology, internal medicine, family medicine, and general practice. Patient information was collected from the hospital's electronic medical record system for the period between January 2016 and December 2021, with all data anonymized. Our research proposal was authorized by the Institutional Research Grants and Ethics Committee (IRG-MHS003-2021), and a waiver for informed consent was obtained. A prevalence-based sample size formula, that is, $n = Z^2P(1 - P)/d^2$ was used to calculate the sample size for the current study.[34] Participants in this study ranged in age from 14 to 85 years and were tested for C-peptides at the hospital upon receiving a clinical diagnosis of T1D or T2D. Other laboratory tests, such as glycosylated hemoglobin (HbA_{1c}) and lipid panel, were also performed and repeated at each subsequent visit. The standard of care at our center is 3 months. The patient was diagnosed with T1D by a clinician on the basis of the following criteria: (1) fasting glucose levels >7.0 mmol/L, (2) HbA_{1c} >6.5%, (3) positive antibody test results (GAD/anti-islet), and (4) need for continuous insulin therapy. The C-peptide assessed at the time of diagnosis of the diabetes type and or within 3 months after diagnosis was considered as baseline. To affirm the baseline, a patient was tested twice for plasma C-peptide during the first year of diagnosis. In addition, demographics, anthropometric measures, clinical and metabolic information, diabetic outcomes, and the medication history of the patients were also recorded.

Inclusion and Exclusion Criteria

Only those patients were included in the study who had been diagnosed with either T1D or T2D by a physician at or before the examination of plasma C-peptide. In addition, those with T1D were thereafter administered insulin for at least 3 years. All the patients who were pregnant or breastfeeding at the time of the C-peptide test, had a history of cancer, had bariatric or metabolic surgery, were on long-term steroid therapy, or did not undergo plasma C-peptide testing in a fasting or random condition were excluded.

Statistical Analysis

Data are expressed as mean (SD) where normally distributed and as median (interquartile range [IQR]) where nonnormally distributed. Mann-Whitney U and Wilcoxon signed-rank tests were performed to assess the difference in plasma C-peptide at baseline in both the T1D and T2D cases. Where applicable, these tests were also performed to assess the significance of difference among baseline and post-baseline characteristics. A receiver operating curve (ROC) analysis was performed to assess the predictive ability of plasma C-peptide in discriminating T1D from T2D. The AUC, specificity, and sensitivity were estimated and plotted. Where the data were missing, mean values were imputed amounting to <2% of the data. Statistical analysis was carried out using R version 4.0.3 (R foundation for Statistical Computing, Vienna, Austria) with tidyverse, dplyr, dlstats, pkgsearch, pROC, ROCR, plotROC, precrec, and ROCit packages. Significance was assessed at $P < 0.05$ and 95% CI.

Results

A total of 313 individuals with diabetes were sorted for data retrieval since January 2016; however, only those who underwent C-peptide testing in fasting were included in this analysis (n = 212). Of the total, 85 (44.8%) were diagnosed with T1D and 127 (55.2%) with T2D. The median duration of diabetes in this analysis was 3.8 (IQR, 3.0–4.5) years.

Patient Characteristics at Baseline

Diabetes was diagnosed at a mean of 35.9 years of age. One hundred twelve (52.8%) of the study participants were men and 100 (47.2%) were women. The median (IQR) HbA_{1c} and fasting glucose levels were 7.4% (6.7%–8.5%) and 7.6 nmol/L (5.6–10.7 nmol/L), respectively. During the entirety of the research, no patient was unaccounted for. On the basis of whether a patient had T1D or T2D, we compared their demographic, clinical, and laboratory characteristics in Table 1. The outcomes provided information about the individual characteristics of each group and served as baseline for further research (Table 1).

Concentrations and Cutoffs for C-Peptide

The median fasting plasma C-peptide concentration for all patients with diabetes in our study was 0.59 (IQR, 0.01–1.14) nmol/L. We observed a clear association between fasting C-peptide levels and the type of diabetes ($P < 0.0001$), with significantly lower concentration of plasma C-peptide in patients with T1D than in patients with T2D ($P < 0.0001$). Figure 1 shows the baseline fasting plasma C-peptide levels among patients with T1D and T2D.

The ROC curve analysis demonstrates that the curve for fasting C-peptide clearly differentiates T1D from T2D (Figure 2). The reported AUC was 97.2%, which supports and is very much in agreement with the aforementioned value. We estimated an optimal fasting C-peptide cutoff point of 0.16 nmol/L for classifying T1D and T2D. Seventy-nine (92.9%) individuals with T1D had a fasting plasma C-peptide level ≤0.16 nmol/L, and 124 (97.6%) individuals with T2D had a fasting C-peptide level >0.16 nmol/L. In addition to this, the reported sensitivity and specificity for the estimated cutoff point during ROC analysis was 92.9% and 2.4%, respectively. Figure 2 shows the ROC analysis with the best predictive cutoff value for C-peptide and its corresponding AUC.

Table 1
The demographic, clinical, and laboratory characteristics of the patients at baseline.

Characteristics at Baseline	T1DM (n = 85)	T2DM (n = 127)
Age at diagnosis (y)*	26.9 (12.9)	41.9 (13.4)
Duration of diabetes (y)*	3.9 (3.5 to 4.6)	3.4 (2.4 to 4.4)
Ethnicity		
UAE national	25 (29.4%)	127 (100%)
UAE nonnationals	60 (70.6%)	—
Sex		
Male	43 (50.6%)	69 (54.3%)
Female	42 (49.4%)	58 (45.7%)
Body mass index (n = 200)		
<18.5 kg/m^2	5 (5.9%)	—
18.5 to <25 kg/m^2*	32 (37.6%)	25 (21.7%)
25 to <30 kg/m^2	28 (32.9)	30 (26.1%)
>30 kg/m^2*	20 (23.5%)	60 (52.2%)
Ever smoked*	18 (21.2%)	45 (35.4%)
Blood pressure		
SBP (mm Hg)	118 (109 to 131)	129 (112 to 138.4)
DBP (mm Hg)	69 (63 to 77)	72.7 (65 to 80)
Diagnostic parameters		
C-peptide (fasting) (nmol/L)*	0.01 (0.003 to 0.05)	1.03 (0.70 to 1.44)
HbA_{1c} (%)*	8.3 (7.2 to 9.9)	7 (6.3 to 7.6)
Plasma glucose (fasting) (nmol/L)	7.7 (5.8 to 11.2)	7.1 (5.3 to 9.4)
Lipid profile		
LDL-C (nmol/L)	2.8 (2.1 to 3.5)	3.2 (2.7 to 4.1)
HDL (nmol/L)	1.4 (1.3 to 1.9)	1.2(1.1 to 1.4)
TG (nmol/L)	1 (0.8 to 1.3)	1.9 (1.2 to 2.6)
TC (nmol/L)	4.6 (3.9 to 5.2)	5.0 (3.5 to 6.0)

Values are presented as n (%), mean (SD), or median (interquartile range). C-peptide = connecting peptide; DBP = diastolic blood pressure; HbA_{1c} = glycosylated hemoglobin; SBP = systolic blood pressure; TC = total cholesterol; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TG = triglycerides; UAE = United Arab Emirates.

* Difference is statistically significant ($P < 0.05$).

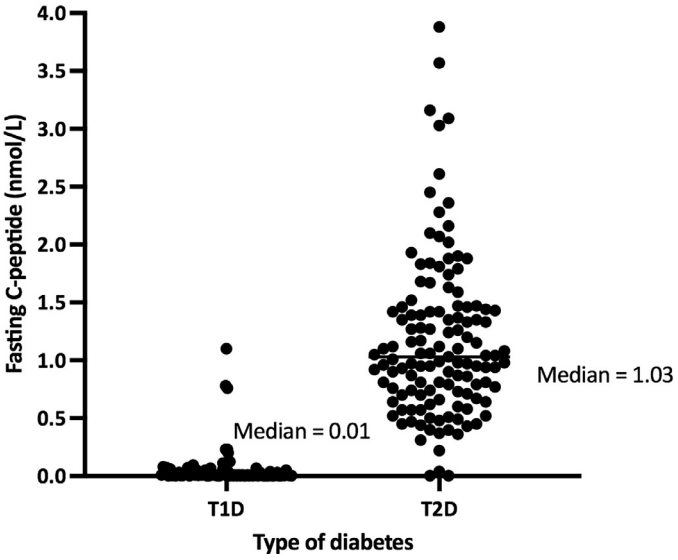

Figure 1. Fasting connecting peptide (C-peptide) concentrations in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). Values are presented as numbers and median (interquartile range).

Discussion

In our study, we measured C-peptide concentrations in the plasma of individuals with T1D or T2D and who were fasting. We discovered a significant relationship between plasma C-peptide concentration and

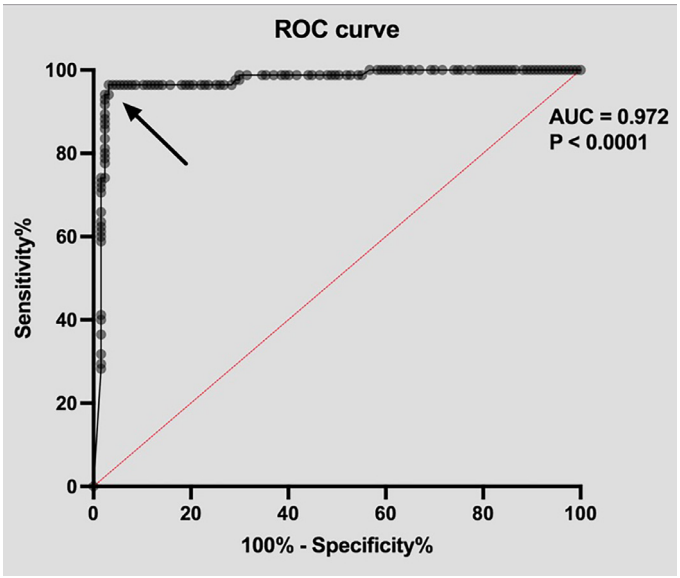

Figure 2. Receiver operator characteristic (ROC) curve for C-peptide. Sensitivity was defined as the ability to designate an individual with disease as positive, Specificity was defined as the ability to designate an individual with no disease as negative. Values are presented as percentage and numbers.

type of diabetes, that is, T1D or T2D. We primarily examined the predictive value of plasma C-peptide in differentiating T1D cases from T2D cases. In our study, we discovered that a plasma C-peptide concentration ≤0.16 nmol/L was highly suggestive of T1D, and a higher concentration in a person who was fasting indicated T2D. On the basis of our findings, we suggest that assessing plasma C-peptide may provide a simple and appropriate method for not only evaluating β-cell function but also efficiently diagnosing T1D and T2D and differentiating patients with T1D from patients with T2D. This discovery could be instrumental in helping physicians to diagnose, classify and treat T1D and T2D more accurately. Furthermore, our findings could guide clinicians in preventing future complications in patients with diabetes because at the young age at diagnosis, the lack of proper treatment with cardiorenal protective therapies over many years (because of misdiagnosis rather than inertia) will have a very significant impact on outcome and prevention of cardiac and renal complications unless classification is performed using C-peptide. In clinical practices, systematic assessments of the diagnosis of T1D with a mindset of changing the treatment to include medication to prescribe solely for T2D rarely occurred, with the assumption that patients will remain on insulin solely or have glycemic control for the rest of their lives. Moreover, young patients presenting with elevated sugar levels and HbA_{1c} are often automatically diagnosed with T1D by the primary care physician or general physician in most cases without additional biomarker investigations. The objective of a biomarker in this case is to systematically and precisely confirm the diagnosis of either T1D or T2D to facilitate therapies with cardiac and renal benefits beyond glycemic control. This would also be relevant in both newly diagnosed diabetes and patients historically diagnosed as T1D.

Diabetes is a serious and potentially life-threatening chronic illness that affects millions of people worldwide. Recent research has shown that in adults with T1D, β-cell failure can begin to appear after as little as 3 to 4 years, a staggering statistic for those newly diagnosed.[35,36] However, it is important to note that clear β-cell dysfunction rarely occurs before the 10-year mark in T2D.[37,38] Several studies have used C-peptide levels to investigate the link between clinical categorization, symptoms, and β-cell performance.[39,40] Moreover, the American Diabetes Association[29] and the European Association for the Study of Diabetes[41] recommend considering C-peptide levels as part of the diagnostic workup, especially in cases where the type of diabetes is uncertain. The National Institute for Health and Care Excellence[42] also acknowledges the role of C-peptide in differentiating between diabetes types, particularly in adults and children with atypical presentations. Clinical guidelines emphasize the importance of integrating C-peptide results with other diagnostic criteria and clinical information to accurately differentiate between T1D and T2D and to guide appropriate treatment decisions. However, very few attempts were made to define the cutoff points for C-peptide to differentiate T1D from T2D. The current research has predominantly used ROC curve analysis to identify an ideal cutoff point for classifying diabetes type. These metrics can be beneficial when attempting to define optimal cutoffs for making a clear distinction between the 2 major types of diabetes. ROC curve analysis could also be used to compute the predictive power of C-peptide to differentiate T1D from T2D.[43,44] The superiority of these advanced analyses has already reached the levels of many other classification schemes for ketosis-prone diabetes. The computed cutoff for C-peptide using ROC analysis in our study is in line with several other published studies in literature, including Ahn et al,[45] who reported a fasting plasma C-peptide cutoff point of less than 0.18 nmol/L; Shahbazian et al,[46] less than 0.21 nmol/L; Becht at al,[47] less than 0.13 nmol/L; Ludvigsson et al,[48] less than 0.2 nmol/L; Katzeff et al,[49] less than 0.04 nmol/L, and Levitt Katz,[50] less than 0.28 nmol/L, all of which were indicating T1D. The minor difference in reported cutoff was obvious because of population differences and study setting differences. However, the difference is minimal, and all studies reported levels either <0.2 nmol/L or close to it, which is comparable with our estimated cutoff point. Contrary to our findings, fewer studies have reported slightly higher cutoff points, that is, <0.5 nmol/L (Thunander et al[51]), <0.42 nmol/L (Berger et al[31]), and <0.35 nmol/L (Kamal et al[52]), for fasting C-peptide and predicting T1D instead of T2D. In addition to this, we examined concomitant glucose levels in plasma to rule out the phenomenon of falsely low C-peptide levels in the setting of hypoglycemia or severe glucose toxicity. We also observed the superior predictive power of the fasting C-peptide cutoff point compared with other published studies with an AUC of 82% to 89% and sensitivity of 92% to 98%. We measured C-peptide in the plasma of patients with diabetes who were fasting overnight or for 8 hours. Although the gold standard measure of endogenous insulin production is obtained by measuring the fasting blood C-peptide level in response to a standard stimulus, such as a mixed meal (mixed meal tolerance test), this method is impractical for application in clinical settings. However, a post-home meal urinary C-peptide creatinine ratio and fasting blood C-peptide provide good estimates of the gold standard with excellent sensitivity and specificity in classifying the diabetes type.[53] Relying solely on fasting C-peptide levels to differentiate between T1D and T2D can be overly simplistic and may not always provide accurate results. An alternative to performing the test is using random C-peptide as it gives similar sensitivities and specificities to diagnose diabetes.

Historically, biomarkers such as blood autoantibodies against β-cells, including insulin, GAD, islet antigen-2, and zinc transport 8, were used to detect T1D, which was difficult to test because of accessibility issues. Furthermore, other antigen-specific autoantibodies have been reported in literature, although they either occur seldom or have been inadequately validated and are not used for prediction. The human leukocyte antigen (HLA) and genetic markers are also used to predict T1D; however, they are not widely available in routine clinical procedures.[54,55] Instead, C-peptide is a readily available test with superior sensitivity and specificity that can accurately distinguish and diagnose T1D. Alongside, our findings have the potential to modernize diabetes classification and its care management. We found that plasma C-peptide testing can be used confidently by physicians for diagnosing the accurate diabetes type and specially to confirm T1D in middle-aged adults or in those in honeymoon period (a time that some patient with T1D go through shortly after being diagnosed) of age and that ultimately will lead to better management of diabetes. Our research not only has the potential to boost physician confidence in using this biomarker but also aids in providing better care management for patients with diabetes.

Recent studies revealed important relations between C-peptide concentrations in plasma and the characteristics of patients with T1D. Individuals with lower levels of plasma C-peptide were more likely to develop T1D in prediagnostic state, whereas those with higher levels of C-peptide had features more closely associated with T2D.[47,52] Our findings on the fasting plasma C-peptide level correspond to and support the above statements. This discovery could be instrumental in helping physicians diagnose, classify, and treat T1D and T2D more accurately. Despite this, it has become more difficult to identify T1D or T2D in adults upon presentation. These obstacles have also been increasingly reported among adolescents and elderly patients, where autoimmune diabetes, also known as T1D, is as prevalent in younger age groups.[50,51] Under such circumstances, age, body mass index, ketoacidosis, and other symptom-based classification schemes may require additional classification criteria or better tools to effectively differentiate between the 2 major types of diabetes. Relying on only one's clinical judgment would not be enough and thus demand additional evidence-based criteria to classify diabetes type accurately. Our study's findings strongly recommend that plasma C-peptide concentrations be incorporated in devising these guidelines.

C-peptide has been uniquely proven as a crucial and superior biomarker in identifying diabetes type when evaluated[47,56] and in combination with additional clinical characteristics such as age at diagnosis, body mass index, GAD antibody, anti-islet autoantibodies status, and family history.[51,57] However, the use of fasting plasma C-peptide in both scenarios (individually and in combination) affirms its importance for routine clinical practices. The measurement of C-peptide not only aids in identifying the correct diabetes type but also helps in determining the cause of hypoglycemia, monitoring insulin production levels, and assessing the responses to the applied therapy. As such, it will serve as an invaluable tool for health care providers in managing diabetes care effectively.

Although clinical diagnosis of T1D or T2D in adults is frequently difficult, measuring plasma C-peptide levels, particularly when fasting, may aid in accurate categorization. Our findings have revealed vital information concerning C-peptide's prognostic role in this regard. Based on our findings, C-peptide is a vital quantitative measure that not only assists clinicians in differentiating patients with T1D more accurately from those with the other major types but also assesses insulin secretion and β-cell function. Our research has the potential to significantly improve the diagnosis and treatment regimen of T1D as well as T2D care management. While having the potential to improve patient outcomes, a resourceful plan could be initiated to develop a healthier and better clinical diabetes care management system by evaluating C-peptide concentrations in plasma of patients. Therefore, laboratory measures/indices of fasting plasma C-peptide will certainly guide appropriate allocation of health care resources. The results of this study may provide valuable information to endocrinologists and other clinicians in deciding between a diagnosis of T1D and T2D, as well as help guide clinical decisions regarding treatment options for a specific diabetes type.

Strengths

To our knowledge, this is the first study in the MENA region highlighting the role of C-peptide in diabetes classification. We have opted for an advanced approach of ROC curve analysis to estimate the predictive ability of C-peptide in differentiating T1D from T2D. The estimated cutoff point will certainly help in accurately classifying diabetes and will rule out the approach of routine clinical judgment in the region, especially in those scenarios and periods where it is always difficult to diagnose the diabetes type. Quantifying the cutoff for C-peptide is among the vital strengths of this study that will provide a better treatment plan in diabetes care management. Also, we evaluated concomitant glucose levels to rule out the phenomenon of falsely low C-peptide values in the setting of hypoglycemia or severe glucose toxicity. Moreover, C-peptide testing could be included in postulating an evidence-based guideline that differentiates T1D from T2D.

Limitations

Our study has some limitations, including selection bias due to the retrospective design, and low C-peptide levels could be indicative of low pancreatic reserves due to other causes, and quantifying these reasons requires additional resources and time.

Conclusions

We concluded that fasting plasma C-peptide is related to the classification of diabetes. Its low plasma concentration has been shown to be quite accurate in identifying, diagnosing and differentiating T1D from T2D. T2D can easily be ruled out if the fasting C-peptide level is <0.16 nmol/L at the time of diagnosis.

Declaration of competing interest

None.

CRediT authorship contribution statement

Sajid Iqbal: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Abdulrahim Abu Jayyab:** Supervision, Resources, Project administration, Methodology, Data curation, Conceptualization. **Ayah Mohammad Alrashdi:** Validation, Resources, Investigation, Formal analysis, Data curation. **Syed Shujauddin:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Josep Lluis Clua-Espuny:** Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Silvia Reverté-Villarroya:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

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