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Insulin secretion capacity as a crucial feature to distinguish type 1 from type 2 diabetes and to indicate the need for insulin therapy - critical discussion of the ADA/EASD consensus statement on the management of type 1 diabetes in adults

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Abstract:	In the recently published consensus statement on the treatment and management of type 1 diabetes issued by experts from the American (ADA) and European (EASD) diabetes societies, measurement of endogenous insulin secretion using fasting C-peptide is recommended as a diagnostic criterion. In contrast, our group recently suggested fasting C-peptide/glucose ratio (CGR) for the determination of endogenous insulin secretion. In addition, this ratio may turn out as a potential decision aid for pathophysiologically based differential therapy of diabetes. In this comment, the following points will be discussed: i) C-peptide glucose ratio (CGR) as the basis of differential diagnosis of type 1 diabetes, ii) CGR as the basis of treatment decision for or against insulin in diabetes, and iii) the ease of application of CGR in clinical practice. The use of CGR may complement the ADA/EASD recommendations and should provide a practical application in clinical practice.

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Andreas Fritsche Tübingen, 19.11.2022

Sehr geehrte Frau Sabine Klee, sehr geehrter Herr Professor Müssig,

vielen Dank für Ihre email vom 12.11.2022. Sie schreiben dort:

„Ich habe bezüglich Abbildung 1 die Bildrechteabteilung des Verlags kontaktiert. Um die Abbildung 1a nutzen zu können, müsste bitte folgende Vorgehensweise eingehalten werden:
In die Legende muss die bibliographische Angabe (nicht nur eine Literatur-Ziffer), und ans Ende der Legende für Abb. 1a [rerif]. Es wäre günstig, wenn Abb. 1a und b zu Abb. 1 und 2 umnummeriert werden könnten.

Ich habe nun die Abbildung Figure 1a und 1b als Figure 1 und 2 umnummeriert und die ehemalige figure 2 in figure 3 umnummeriert.
Weiterhin habe ich wie verlangt in der Legende zu figure 1 die vollständige bibliographische Angabe eingefügt.
Zudem habe ich die Legende zu figure 3 noch präzisiert und im Text des Manuskripts noch Einheiten für C-Peptid und Glukose eingefügt und einen redundanten Halbsatz (bei Punkt 2) gestrichen.
Figure 1 hat eine schlechte Qualität, da ich Sie aus dem PDF der Veröffentlichung in Diabetologia herauskopieren musste, und die Qualität dort schon schlecht war. Darf ich darum bitten, bei Diabetologia um die Originalabbildung in hoher Qualität anzufragen?

Ich möchte nochmals darauf hinweisen, dass ich einen eingeladenen Kommentar in deutscher Sprache geschrieben habe mit dem Titel: „Einfache Einteilung der Subtypen des Diabetes in der Praxis“ für „Der Diabetologe“. Der Kommentar ist für ein vom DZD herausgegebenes Sonderheft. Zu Ihrer Information habe ich das bei „Der Diabetologe“ eingereichte Manuskript beigefügt, in dem ich natürlich das Manuskript ECED-06-2022-0167 zitieren werde, wenn es von ECED akzeptiert wird.
Die figures 2 und 3 aus ECED sind in ähnlicher, aber abgewandelter Form auch im Beitrag für „Der Diabetologe“ enthalten. Ich bitte sie freundlich zu prüfen, ob dies so in Ordnung für den Thieme Verlag ist.

Mit freundlichem Gruß A. Fritsche

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Insulin secretion capacity as a crucial feature to distinguish type 1 from type 2 diabetes and to indicate the need for insulin therapy

Critical discussion of the ADA/EASD consensus statement on the management of type 1 diabetes in adults

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Abstract

In the recently published consensus statement on the treatment and management of type 1 diabetes issued by experts from the American (ADA) and European (EASD) diabetes societies, measurement of endogenous insulin secretion using fasting C-peptide is recommended as a diagnostic criterion. In contrast, our group recently suggested fasting C-peptide/glucose ratio (CGR) for the determination of endogenous insulin secretion. In addition, this ratio may turn out as a potential decision aid for pathophysiologically based differential therapy of diabetes. In this comment, the following points will be discussed: i) C-peptide glucose ratio (CGR) as the basis of differential diagnosis of type 1 diabetes, ii) CGR as the basis of treatment decision for or against insulin in diabetes, and iii) the ease of application of CGR in clinical practice. The use of CGR may complement the ADA/EASD recommendations and should provide a practical application in clinical practice.

Endogenous insulin secretion is the critical pathophysiological component in diabetes mellitus [1]. It is determinant both for the conventional classification into type 1 and type 2 diabetes mellitus [1,2] and in the more recent classification according to cluster-related subtypes [3,4]. It can be measured simply as the C-peptide/glucose ratio (CGR) [5]. It is suggested that the ADA/EASD consensus statement on the treatment and management of Type 1 should be amended to include the CGR determination. In this regard, 3 points are discussed below.

1.) C-peptide glucose ratio (CGR) as a basis for differential diagnosis of type 1 diabetes

In the ADA/EASD Consensus Statement, a flowchart for the investigation of suspected type 1 diabetes in newly diagnosed adults is provided (see Figure 1~~a~~). The critique of this scheme is summarized in the flowchart shown ~~in parallel~~ in Figure ~~1b~~2. The primary aim of the differential diagnosis of diabetes is to separate type 1 diabetes from type 2 diabetes. It is important to diagnose the fundamental and therapy-decisive pathophysiology of type 1 diabetes, namely the absolute and life-threatening insulin deficiency. Thus, the items listed in Figure 1~~a~~, such as age at manifestation and monogenetic forms of diabetes with associated genetic analyses, recede into the background. In particular, the age limit of 35 years, which induces a different type 1 diabetes incidence and different diagnostic approach in the flowchart of the ADA/EASD group, is unfounded because, according to a recent study, 42% of all new type 1 manifestations occur after 30 years of age [6].

The key point in the differential diagnosis is the measurement of endogenous insulin secretion since type 1 diabetes is defined as severe insulin deficient (with or without autoimmunity). However, this deficit is inadequately defined with C-peptide measurement alone, as suggested by the ADA/EASD Consensus Statement. C-peptide level is strongly correlated with glucose level, since glucose is the physiological trigger for insulin secretion. Thus, the C-peptide value must be adjusted to the currently prevailing glucose value, preferably by dividing the C-peptide value (in pmol/l) by the simultaneously measured glucose value (in mg/dl, C-peptide-glucose ratio CGR) [5,7]. The measurement is best

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carried out in the fasting state, as there is less fluctuation in the values and postprandial triggers of insulin secretion such as incretins play a lesser role.

As already pointed out in the recently published commentary on the CGR [5], an insulin deficiency and thus a need for insulin therapy must be assumed if the CGR is below 2.

In order to demonstrate the superiority of the CGR compared to a pure measurement of C-peptide, one only needs to assume a C-peptide value of 300 pmol/L, which excludes type 1 diabetes according to the ADA/EASD Consensus. If the blood glucose value measured at the same time is 90 mg/dl, sufficient insulin secretion can be assumed. However, if the blood glucose is 200 or even 250 mg/dl (CGR 1.5 /1.2) at the same C-peptide level of 300 pmol/L, a severe insulin deficiency is present and type 1 diabetes must be suspected.

It is important to note that many people with a new onset type 1 diabetes still may have a residual β-cell function at the time of diagnosis and during the remission phase. Therefore, in these situations C-peptide-Glucose Ratio will misclassify people with type 1 diabetes and residual β-cell function. Here, repeated measurements of CGR and an additional measurement of antibodies might be useful as shown in figure ~~1b~~2. However, it has to be emphasized that the main purpose of measuring the C-peptide-to-glucose ratio is to predict the need for insulin therapy (see paragraph 2).

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2.) C-Peptide Glucose Ratio as a basis for Insulin Therapy Decision in Diabetes

Differential diagnosis of diabetes mellitus is important, but even more important is the subsequent treatment decision [7]. If there is an absolute lack of endogenous insulin secretion, treatment with insulin is necessary, whether autoantibodies are present or not. In the case of ~~autoantibody positivity in the context of a so-called LADA or in~~ people with type 1 diabetes manifestation at an older age, a very long remission phase with relatively high endogenous insulin secretion (high CGR) may be present. Depending also on the HbA1c value, insulin therapy can be postponed. Alternatively, low-dose insulin therapy can be started with once-daily basal insulin. In Figure ~~1b~~2, the blackening of the

"therapy bar" indicates that the lower the CGR, the more likely insulin therapy is considered or mandatory. The limits of a CGR of less than 2, which argues for insulin therapy, and greater than 5, which argues against insulin therapy, should not be viewed in absolute terms, but rather as a guidance to aid treatment decisions.

The classification into subtypes of diabetes, which should enable precision diabetology, has so far been very limited by the different methods and the complex investigations required and the large number of parameters for classification and phenotyping [8,9]. As recently pointed out by our group [5], CGR provides a therapeutic decision aid that is useful in everyday clinical practice and can actually lead to more precise diabetology. However, there is a substantial overlap in C-peptide to glucose ratio between the types of diabetes [5] indicating that this is not an accurate way of differentiating across these endotypes of diabetes.

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3.) C-peptide glucose ratio in clinical practice

Beside the homeostasis model assessment of b-cell function (HOMA-b) index, there are other published indices using fasting C-peptide and fasting glucose in different complicated formulas with different multiplyers. Among them are the secretory units of islets in transplantation index (SUIT) and the fasting serum C-peptide immunoreactivity index (CPI) [7]. This makes such indices rather unusable in everyday clinical practice. In contrast, fasting C-peptide-to-glucose-ratio is easy to determine by mental calculation. However, different units of measurement are reported by different laboratory providers (C-peptide in pmol/l or µg/L), blood glucose in mmol/l or mg/dl). Figure ~~2~~ 3 allows the simple determination of the CGR for different units by means of a nomogram. From this, a differential therapy may be derived, which is explained in more detail in our previous commentary [5]. Briefly, at a CGR <2 (C-peptide in pmol, glucose in mg/dl), pink box ~~Fig2~~Fig3), insulin therapy is needed, and the lower the CGR, the more so with a basal and bolus insulin regimen. With a CGR between 2 and 5 (blue box ~~Fig2~~Fig3), basal insulin therapy in combination with other antidiabetic agents is necessary. The type of non-insulin antidiabetic agents depends on cardiovascular risk

factors and concomitant diseases. With a CGR above 5 (green field ~~Fig2~~Fig3), insulin therapy is usually not necessary; sufficient endogenous insulin secretion exists. Non-insulin antidiabetic agents are then used, again depending on the presence of cardiovascular risk factors [5]. However, the focus of the differential diagnostic and differential therapeutic approach always is to use CGR to quickly identify those patients who need immediate insulin therapy. This can be easily done by the offered diagram. The question of endogenous insulin deficiency and the need for insulin therapy also arises repeatedly during the course of chronic progressive type 2 diabetes and can also be easily assessed with CGR determinations during the course of the disease.

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Summary

According to international consensus, insulin secretory capacity is an important factor in the differential diagnosis and differential therapy of diabetes mellitus [1]. Simple ratios (CGR) and nomograms as presented here help to determine insulin secretory capacity in clinical practice. The potential benefit of the additional cost and administrative work in calculating the C-peptide to glucose ratio needs to be determined in prospective studies before it may be introduced into guidelines.

Legend Figure 1 ~~a~~

ADA/EASD Consortium flow chart ~~(2, with permission)~~ for screening for suspected type 1 diabetes in newly diagnosed adults, based on data from white European populations. Figure with permission from: ~~-~~*Holt RIG, DeVries JH, Hess-Fischl A et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2021; 64: 2609-2652.*

Legend Figure ~~1b~~2

Simplified alternative proposal for testing suspected type 1 diabetes in newly diagnosed adults

Legend Figure ~~2~~ 3

Nomogram for simple determination of fasting C-peptide-glucose ratio (C-peptide in pmol/l, glucose in mg/dl) as a measure for estimation of endogenous insulin secretory capacity. Different units of measurement are reported by different laboratory providers (C-peptide in pmol/l or µg/L), glucose in mmol/l or mg/dl). The normogram can be used for easy and simple determination of the CGR for different units. C-peptide was measured with Siemens ADVIA Centaur XPT.

Pink field: CGR<2, insulin secretion deficit. Insulin therapy needed, the lower CGR, the more likely basal-bolus insulin therapy

Blue field: CGR2-5, impaired endogenous insulin secretion. Basal insulin therapy in combination with other antidiabetic agents

Green field: CGR>5, preserved endogenous insulin secretion. Usually no insulin therapy needed, but oral antidiabetic agents and incretin analogues

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Figure 1

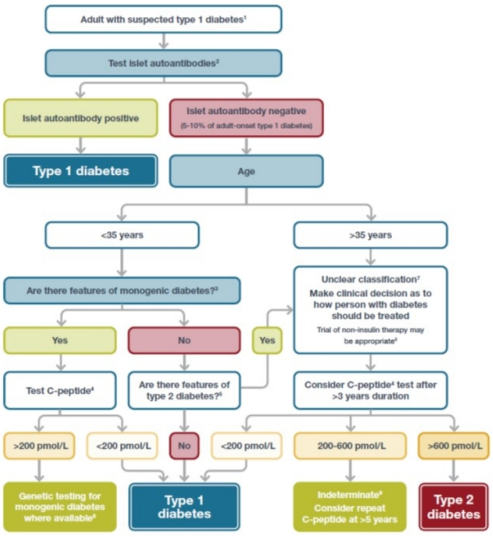

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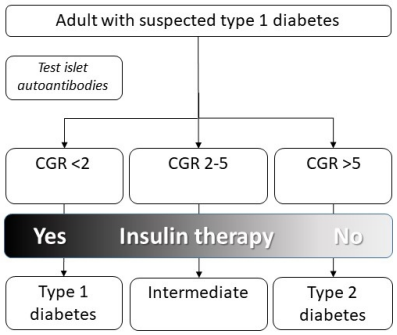
Figure 2



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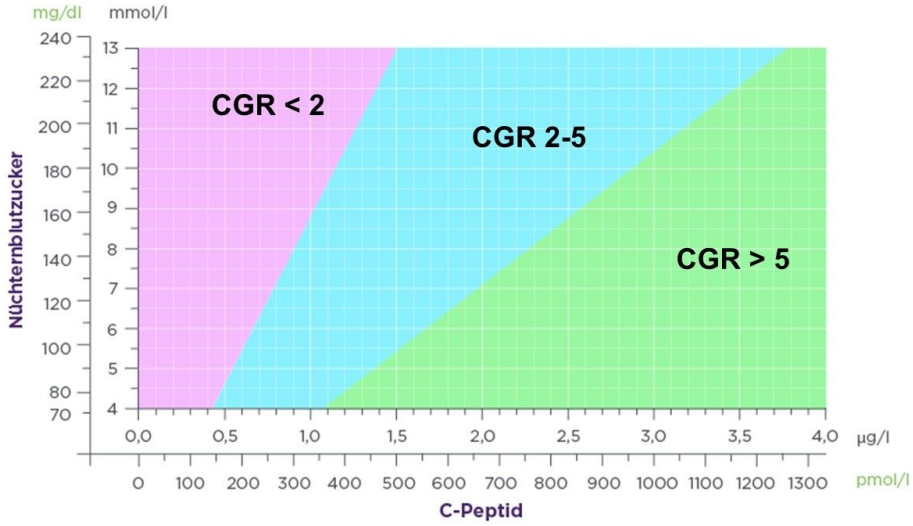

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