Received: 26 September 2022 | Accepted: 5 December 2022

DOI: 10.1111/eci.13934

NARRATIVE REVIEW

WILEY

Leveraging the future of diagnosis and management of diabetes: From old indexes to new technologies

Maria João Meneses[1,2] | **Rita Susana Patarrão**[1] | **Tomás Pinheiro**[3] | **Inês Coelho**[1] | **Nuno Carriço**[2] | **Ana Carolina Marques**[3] | **Artur Romão**[2] | **João Nabais**[4] | **Elvira Fortunato**[3] | **João Filipe Raposo**[1,5] | **Maria Paula Macedo**[1,5]

[1]iNOVA4Health, NOVA Medical School, Faculdade de Ciências Médicas, NMS, FCM, Universidade NOVA de Lisboa, Lisbon, Portugal

[2]DECSIS II Iberia, Évora, Portugal

[3]CENIMAT i3N, Materials Science Department, Faculty of Science and Technology, Universidade NOVA de Lisboa and CEMOP/UNINOVA, Caparica, Portugal

[4]Comprehensive Health Research Centre (CHRC), Departamento de Ciências Médicas e da Saúde, Escola de Saúde e Desenvolvimento Humano, Universidade de Évora, Évora, Portugal

[5]APDP – Diabetes Portugal – Education and Research Center, Lisbon, Portugal

Correspondence
M. Paula Macedo, iNOVA4Health, NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal.
Email: paula.macedo@nms.unl.pt

Funding information
European Commission Marie Skłodowska-Curie Action H2020, Grant/Award Number: 734719; Fundação para a Ciência e a Tecnologia, Grant/Award Number: UIDB/Multi/04462/2020; Portugal2020, Grant/Award Number: ALT20-03-0247-FEDER-113469 and LISBOA-01-0247-FEDER-113469; Sociedade Portuguesa De Diabetologia

Abstract

Background: Diabetes is a heterogeneous and multifactorial disease. However, glycemia and glycated hemoglobin have been the focus of diabetes diagnosis and management for the last decades. As diabetes management goes far beyond glucose control, it has become clear that assessment of other biochemical parameters gives a much wider view of the metabolic state of each individual, enabling a precision medicine approach.

Methods: In this review, we summarize and discuss indexes that have been used in epidemiological studies and in the clinical practice.

Results: Indexes of insulin secretion, sensitivity/resistance and metabolism have been developed and validated over the years to account also with insulin, C-peptide, triglycerides or even anthropometric measures. Nevertheless, each one has their own objective and consequently, advantages and disadvantages for specific cases. Thus, we discuss how new technologies, namely new sensors but also new softwares/applications, can improve the diagnosis and management of diabetes, both for healthcare professionals but also for caretakers and, importantly, to promote the empowerment of people living with diabetes.

Conclusions: In long-term, the solution for a better diabetes management would be a platform that allows to integrate all sorts of relevant information for the person with diabetes and for the healthcare practitioners, namely glucose, insulin and C-peptide or, in case of need, other parameters/indexes at home, sometimes more than once a day. This solution would allow a better and simpler disease management, more adequate therapeutics thereby improving patients' quality of life and reducing associated costs.

KEYWORDS

C-peptide, glycemic variability, HbA1c, indexes, insulin resistance, insulin sensitivity, oral glucose tolerance test, prediabetes, type 2 diabetes

1 | INTRODUCTION

Diabetes is a complex, multiple etiological disease, which comprises multiple organs and includes alterations in various biochemical parameters. Glycemia has been the focus for both diagnosis and monitoring of diabetes. However, it is now largely known that diabetes management goes far beyond glucose control. Being a complex condition, different factors, mediators and mechanisms play a role in sustaining disease progression.[1]

Insulin resistance is the core defect in type 2 diabetes (T2D) and the primary factor in the glucose imbalance in three pivotal tissues: skeletal muscle, liver and adipose tissue. Furthermore, excessive lipid accumulation in cells may lead to insulin resistance leading to compensatory increase in insulin secretion and hyperinsulinemia. The identification of a routinely applicable indicator, simple and reliable markers of disease related to glucose and lipid metabolism, with higher sensitivity and specificity than classical parameters (such as waist circumference [WC], body mass index [BMI] and lipid profile), could be useful not only for diabetes but also for cardiometabolic risk assessment and contribute to promote personalized early interventions in the clinical setting.

In an era of precision medicine, it is fundamental to have a wider view on metabolic disorders such as diabetes and consider other factors involved in glucose homeostasis, as insulin and C-peptide. These values are rarely used in clinical practice, and they are not measured on a daily basis nor in an attempt to monitor disease progression and/or effectiveness of therapeutic.

2 | TYPE 2 DIABETES: GLUCOCENTRIC VISION VERSUS INTEGRATIVE VISION

Glycemia and its surrogate indicator – glycated haemoglobin (HbA1c) are the gold standard to diagnose and monitor disease progression.[2] More recently, continuous glucose monitoring (CGMs) has brought some advances in disease control independently of the type of diabetes, introducing new metrics and enabling the discussion on glucose variability.[3,4] Indeed, this chronic disease is reliant on patient awareness and empowerment for glycemia control.

When Banting and Best firstly reported the effect of insulin based on the pancreatic extracts in 1922, it was revealed that insulin had a '*great potency in controlling carbohydrate and fat metabolism in normal and diabetic animals as well as in patients suffering from diabetes mellitus*'.[5] Due to the difficulty of measuring insulin in plasma, which only occurred in 1960s, all known effects of insulin were based on its capacity to produce hypoglycemia or glucose uptake by isolated organs.[6] In consequence, this phenomenon brought glycemia as a central player for the diagnosis and management of diabetes undermining the role of insulin.

However, over the last years, it has become evident that evaluation of other biochemical parameters gives a much wider view of the metabolic state of each individual. With the concept of precision medicine, and that diabetes has different phenotypic contours,[7,8] it is more important than ever to assess other key parameters involved in diabetes onset and progression, such as insulin, C-peptide and lipid profile, which will aid in determining the most appropriate therapeutic strategy aiming at precision medicine.

Although this need is well-identified and recognized,[9] the implementation of the evaluation of these parameters on a daily basis has failed. This mostly happens due to a lack of quick and unexpensive methods that would allow to do it in point-of-care or at homecare as is the case for glycemia.

Besides the clinical values per se, the usage of surrogate indexes based on insulin, C-peptide or glycemic levels at a specific time should be very important to extract clinically-relevant information.[10,11] Of relevance, and using these values, one can for example assess insulin secretion, which when decreased could result from either defects of β-cell function or a reduction in β-cell mass. On the contrary, insulin sensitivity or insulin resistance, the latter as a result of the incompetence of insulin action to promote glucose uptake or insulin clearance/metabolism, have been also evaluated based on indexes that are still far beyond expected to be used in clinical practice.

For instance, defects in the interplay of insulin secretion, action and metabolism (Figure 1) are not a continuum and some individuals might have a more pronounced insulin-resistant phenotype and others a deficiency in insulin secretion, among other phenotypes.[8] These features may even be altered throughout the day and with the prandial state, meaning that an individual can have an alteration in the fasting that does not mirror the alterations in the postprandial and vice versa. Even further away from common evaluation is insulin metabolism,[12] which is rarely accounted to phenotype an individual and to be of any relevance for therapeutics.

In general, even though the use of different indexes to indirectly assess insulin resistance has been established, they are still laborious and time-consuming and far from patient awareness. In addition, the cut-offs currently used for these indexes vary a lot and comprise vast intervals, which makes them not consensual within the clinical community. Therefore, a new perspective to be incorporated in clinical practice on the usage of these types

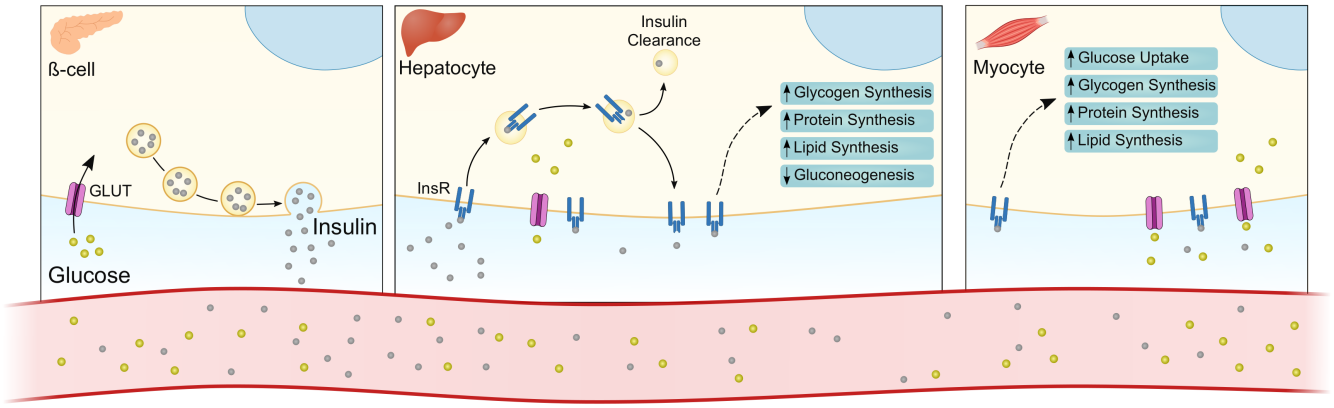

FIGURE 1 Insulin secretion, metabolism and action. Insulin secretion from pancreatic β-cells in response to increased glucose levels encompasses a series of events that results in the fusion of secretory granules with the plasma membrane. After being released to circulation, insulin reaches the liver through the portal vein. Here, insulin is metabolized in the hepatocytes in a process named *insulin clearance*, but it also exerts actions, namely activates glycogen synthesis, decreases gluconeogenic gene expression and increases lipogenic gene expression. After reaching the liver, insulin also reaches other organs such as the muscle, where it leads to increased glucose uptake and glycogen synthesis, among others.

of indexes should be addressed to take advantage of all the available tools to manage diabetes and its associated comorbidities.

3 | LIFESTYLE AND THERAPEUTICS

Lifestyle interventions based on physical activity and/or diet are determined for improved glycemic control cardiometabolic health and prevention management of diabetes complications. There are numerous intervention programs and, they are scarcely based on the phenotypic metabolic profile of an individual. Usually, the interventions are based on a trial-and-error approach. It is known that different nutrients have a dissimilar impact on glycemic levels in two individuals that have the same glucose excursion during an oral glucose tolerance test (OGTT).[13] The distinctive postprandial plasma milieu, glycemia and lipidemia are characteristics of different pathophysiological mechanisms, which can be attributed to genetic and environmental features.[8] The same rational can be ascribed to different physical activities. Therefore, before understanding the milieu thru omics data, it is necessary to pinpoint which type of mechanisms are altered in a specific patient since the milieu is a resultant of changes in mechanisms. This does not take away the relevance of understanding the outcome of the changes in mechanisms. Moreover, in a more accurate and complex picture, carbohydrates can be converted to lipids and the other way around depending on the type of altered mechanisms and diet.

The same rational applies to therapeutic interventions. The concept of precision medicine has been recommended, which goal is to achieve the most effective approach for a similar group of patients regarding genetic, environmental, lifestyle and clinical factors, within others.[14] Therapeutic guidelines arise to first address glycemic control and subsequently the reduction in complications/comorbidities. An interesting twist is that nonalcoholic fatty liver disease (NAFLD) can be viewed as either driver or consequence of T2D. So, should we address NAFLD or T2D first? Or does a specific individual have hepatic or skeletal muscle insulin resistance? In the milieu, it is expected that hepatic insulin resistance drives preferentially fasting hyperglycemia and skeletal muscle insulin resistance impacts postprandially. The lipid profile of one case might be completely different from the other. Therefore, should we address both cases in the same way? To achieve precision medicine, the therapeutic approach is chosen subsequently phenotyping the patient and identifying the individual specificities. For example, in precise medicine of T2D, an individual with poorly controlled glycemia with hypertension (without atherosclerotic disease or chronic kidney disease), when on metformin, can be prescribed with one of five drugs: DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors, thiazolidinediones, sulfonylureas. Presently, each doctor will decide to take into account the broader view of the guidelines. Which is the best treatment for a patient in this condition? Should we just be aiming at putting him/her in a good track for glycemic control without understanding which mechanisms are compromised? By using indexes, we understand mechanisms and together with the milieu content, we can allocate one individual into a group of people sharing common features of the overall metabolic condition, which will respond well to a defined therapeutic.[8]

4 | USAGE OF INDEXES FOR ASSESSING INSULIN SECRETION, METABOLISM AND SENSITIVITY/RESISTANCE

Hitherto, quantifying insulin secretion, metabolism and resistance in humans, has been of great importance for epidemiological studies, and clinical and basic science investigation, using direct and indirect methods of varying complexity. However, the use of algorithm-derived methods needs validity and reproducibility, and the cost is also an important factor to be considered when choosing a particular method.[15] These methods may rely on the single (one timepoint) analysis of glucose, insulin and/or C-peptide or on dynamic testing (several timepoints). Although less informative than dynamic tests, single measurements are more common in clinical practice due to their simplicity. The single measurements of glucose, insulin and C-peptide are usually performed under fasting conditions (basal state). In healthy subjects, the fasting condition represents a basal steady-state where glucose is homeostatically maintained in normoglycemia such that insulin levels are not significantly changing and hepatic glucose production is constant. Basal insulin secretion by pancreatic β-cells determines a relatively constant level of insulinemia that will be lower or higher in accordance with insulin sensitivity/resistance, such that hepatic glucose production matches whole-body glucose disposal under fasting conditions. Methods based on fasting glucose and insulin concentrations reflect primarily hepatic insulin sensitivity/resistance. Under most conditions, hepatic and skeletal muscle insulin sensitivity/resistance is proportional. However, in the diabetic state with fasting hyperglycemia, fasting insulin levels are inappropriately low and insufficient to maintain euglycemia. Another limitation for the measurement of fasting plasma insulin is the pulsatile mode of insulin secretion (pulses with a periodicity of 10–15 min and ultradian oscillation periods of 1–3 h). The periodicity, amplitude and ultradian oscillations of insulin pulses vary in the fasting state and are altered in subjects with dysmetabolism.[16] Thus, these specificities of insulin secretion should be considered when assessing the most useful evaluation methods and/or indexes.

Glucose disposal after a meal is mediated by a complex network that includes absorption, glucose effectiveness, neurohormonal and incretin actions, insulin secretion and metabolic actions of insulin that primarily determine the balance between peripheral glucose utilization and hepatic glucose production.

Blood glucose measurements in the postprandial state are usually performed in specific timepoints of the OGTT or the standardized meal tolerance test (MTT).[17] These methods consider both fasting steady-state and dynamic postload, either glucose or meal, plasma glucose and insulin levels. Although the oral route of glucose/meal delivery is more physiological, the poor reproducibility of the OGTT and standardized MTT due to variable glucose absorption, splanchnic glucose uptake and additional incretin effects needs to be incorporated in a new view.

Since several guidelines state that 'the OGTT is not recommended for routine clinical use', the MTT, which is a 'physiologic' variant of OGTT, becomes an interesting alternative for an in-depth assessment of glucoregulation. The MTT offers several advantages, namely: (i) lack of artifactual postload hypoglycemia, thus making this test suitable for the study of postprandial hypoglycemia, usually due to high insulin sensitivity, or in a context of insulin resistance to hyperinsulinism; (ii) use of a physiologic stimulus triggering a cephalic phase proportional to palatability scores; and (iii) possibility to measure insulin sensitivity with a modified algorithm based on the minimal model as well as glucose effectiveness and insulin secretion. The MTT can represent a simple procedure, less unpleasant for the subject than any other assessment of glucose metabolism (including the standard OGTT) while providing both a physiologic picture of glucoregulation and a sophisticated analysis of it in terms of insulin sensitivity, glucose effectiveness and insulin secretion.

5 | INSULIN SECRETION

There are several methods used to evaluate insulin secretion and β-cell function, namely HOMA-B, insulinogenic index (IGI) and blood C-peptide to glucose ratio (Table 1). Indeed, besides glucose and insulin, some insulin secretion-related indexes consider C-peptide, a well-known marker of β-cell function. C-peptide is split from insulin in the beta-cell secretory granules and co-secreted with insulin.[18] Since insulin, but not C-peptide, is extracted by the liver, serum and urinary C-peptide levels reflect the absolute amount of endogenous insulin secretion.[19] However, as the kidney is a major site of C-peptide clearance through glomerular filtration and uptake from peritubular capillaries, it is not a good indicator of insulin secretion and β-cell function in cases of nephropathy.[19,20] Usually, C-peptide is measured after overnight fasting. As the plasma glucose level is relatively stable during fasting, insulin secretion is assumed to be stable. Thus, the assessment of β-cell function using fasting samples is reproducible and more easily comparable within and between individuals. However, insulin secretion increases in a postprandial state. Since in a postprandial state, not only the higher plasma glucose level but also incretin effects stimulate insulin secretion,

TABLE 1 Indexes of insulin secretion, resistance and/or metabolism derived from fasting and MTT/OGTT measurements.

Index	Formulae	Advantages	Limitations	Ref.
Insulin secretion and β-cell function				
HOMA-β	$\frac{360\times I_0}{G_0\ (mg/dl)-63}$ or $\frac{20\times I_0}{G_0\ (mmol/L)-3.5}$	Simple Minimally invasive Predicts fasting steady-state G and I levels[143]	Only fasting	23
Insulinogenic index (IGI)	$\frac{I_{30}-I_0}{G_{30}-G_0}$	Detects early insulin response to glucose changes; Measures postprandial β-cell function	More than one timepoint	143
C-peptide to glucose ratio	$\frac{C-peptide}{Glucose}\times 100$	Fasting and postprandial Assesses β-cell function, even in patients under insulin therapy	Alterations in C-peptide metabolism and/or therapeutic interventions that act on β-cells may induce a bias	144
Urinary C-peptide to Creatinine ratio (UCPCR)	$\frac{C-peptide\ (nmol/L)}{Creatinine\ (mmol/L)}$	Noninvasive Stable	Inappropriate for individuals with kidney disease	32
Insulin resistance/sensitivity				
Gutt index Insulin sensitivity index (ISI)	$\frac{75.000+(G_0-G_{120})\times 0.19\times BW}{120\times\frac{G_0+G_{120}}{2}\times\log\left(\frac{I_0+I_{120}}{2}\right)}$	Reliable Good at predicting diabetes onset	Several timepoints Difficult to calculate	75
Cederholm index	$\frac{75.000+(G_0-G_{120})\times 1.15\times 180\times 0.19\times BW}{120\times G_{mean}\times\log(I_{mean})}$	Reliable Good at predicting diabetes onset	Several timepoints Difficult to calculate	74
Matsuda index	$\frac{10{,}000}{\sqrt{G_0\times I_0\times G_{mean}\times I_{mean}}}$	Assesses both hepatic and peripheral tissue sensitivity to insulin	Weak index for people with diabetes	73
Oral glucose insulin sensitivity (OGIS)	$f(G_0, G_{90}, G_{120}, I_0, I_{90}, I_{120}, D_0)$, where D_0 is the oral glucose dose (g/m^2 body surface area) Calculated in a spreadsheet or in a web OGIS calculator	Alternative to hyperinsulinemic euglycemic clamp Can be used with both common and SI units	Time-consuming Multiple timepoints	70
Homeostasis model assessment (HOMA-IR)	$\frac{G_0(mg/dl)\times I_0}{405}$ $\frac{G_0(mmol/L)\times I_0}{22.5}$	Consistent Precise Minimally invasive	Only fasting Cannot be used when glucose <3.5 mmol/L	22
HOMA2-IR	Calculated with a spreadsheet	One single sample	Only fasting	53
HOMA-AD	$\frac{G_0\times I_0}{Adiponectin}$	One single sample	Only fasting	97
Duncan index Fasting insulin resistance index (FIRI)	$\frac{G_0\times I_0}{25}$	Similar to HOMA-IR but can be used with any value of glucose One single sample	Only fasting	77
Quantitative insulin sensitivity check index (QUICKI)	$\frac{1}{\log(I_0)+\log(G_0)}$	One single sample	Only fasting	62
Fasting glucose to insulin ratio	$\frac{G_0}{I_0}$	Simple One single sample	Only fasting	52
Insulin metabolism				
Insulin clearance (IC)	$\frac{C-peptide\ AUC}{Insulin\ AUC}$		Need of an MTT or OGTT	145

(Continues)

TABLE 1 (Continued)

Index	Formulae	Advantages	Limitations	Ref.
Disposition index (DI)	$(S_I \times AIR_g)$		Difficult to calculate	84
Oral disposition index (DI_O)	$\frac{\frac{I_{30}-I_0}{G_{30}-G_0}}{I_0}$	Alternative to DI		86
Other indexes				
Visceral adiposity index (VAI)	$VAI_{men} = \left(\frac{WC}{39.68+1.88\times BMI}\right)\times\left(\frac{TG}{1.03}\right)\times\left(\frac{1.31}{HDL}\right)$ $VAI_{women} = \left(\frac{WC}{39.68+1.88\times BMI}\right)\times\left(\frac{TG}{0.81}\right)\times\left(\frac{1.52}{HDL}\right)$	Useful surrogate marker for visceral adiposity	Different formula for men and women	100
Lipid accumulation product (LAP)	$LAP_{men} = (WC-65)\times TG_0$ $LAP_{women} = (WC-58)\times TG_0$	Simple	Only fasting Different formula for men and women	105
Triglycerides and glucose index (TyG)	$\ln\frac{TG_0\left(\frac{mg}{dl}\right)\times G_0\left(\frac{mg}{dl}\right)}{2}$	Simple One single sample	Only fasting Needs further validation in diabetes	90
Fatty liver index (FLI)	$\frac{e^{0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745}}{1+e^{0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745}}\times 100$	Simple Minimally invasive		112
Fibrotic nonalcoholic steatohepatitis index (FNI)	$\frac{e^{-10.33+2.54\times\ln(AST(U/L))+3.86\times\ln(HbA1c(\%))-1.66\times\ln(HDL(mg/dl))}}{1+e^{-10.33+2.54\times\ln(AST(U/L))+3.86\times\ln(HbA1c(\%))-1.66\times\ln(HDL(mg/dl))}}$	Simple Minimally invasive Validated in diabetes		121,122

Abbreviations: AST, aspartate aminotransferase; AUC, area under the curve during the OGTT; BW, body weight; G, glucose; GGT, ɣ glutamyl transferase; G_x, glucose values in the x timepoint of the OGTT; HbA1c, glycated haemoglobin; HDL, high-density lipoproteins; I, insulin; I_x, Insulin values in the x timepoint of the OGTT; OGTT, oral glucose tolerance test; TG, triglycerides; WC, waist circumference.

postprandial C-peptide levels more likely reflect the maximal insulin secretory capacity compared with fasting C-peptide level, namely in patients with T2D.

5.1 | Insulinogenic index

Insulinogenic index estimates insulin secretion and can be calculated from the OGTT data, i.e. the ratio between the increase in plasma glucose and insulin levels 30 min after the glucose load. The IGI at 30 min of OGTT is frequently used to assess β-cell function. Although there is no gold standard for β-cell function, C-peptide is a much better marker of pancreatic activity than peripheral insulin. If IGI is used for β-cell function during OGTT, indexes of insulin resistance/sensitivity such as HOMA should be avoided, because they are strongly influenced by the fasting measurements, included also in IGI. IGI is an acceptable index of β-cell function and is able to discriminate among subjects with various degrees of glucose tolerance.[21]

5.2 | HOMA-β

HOMA-β, in turn, produces a single readout of β-cell function.[22] It is a surrogate marker that only requires paired fasting insulin and glucose measurements, so it has been used in large epidemiological and pharmaceutical studies. However, HOMA-β is not an appropriate model for subjects on exogenous insulin nor to evaluate and compare drugs with similar effects on blood glucose but different modes of action (e.g. DPP4 inhibitors vs. sulfonylureas).[22–24] Indeed, it can be used in subjects on insulin secretagogues such as sulfonylureas, but the results need to be interpreted accordingly.[25]

5.3 | C-peptide to glucose ratio

As glucose is a major stimulator of insulin secretion, blood C-peptide to glucose ratio allows for a more accurate assessment of β-cell function than only C-peptide, especially in patients with hyperglycemia.[26,27] Postprandial but not fasting blood C-peptide to glucose ratio significantly correlated with disposition index (DI) (see below) calculated by glucose clamp, reflecting correct β-cell function adjusted for insulin sensitivity.[27,28] As insulin secretion is higher in the postprandial state, the use of the postprandial blood C-peptide to glucose ratio allows for the analysis of β-cell functional capacity.[29] Indeed, it was already described that postprandial blood C-peptide to glucose ratio anticipated not only the need for multiple daily insulin injections in patients with type 2 diabetes[30] but also predicted better treatment strategies.[31]

5.4 | Urinary C-peptide to creatinine ratio

Urinary C-peptide to creatinine ratio (UCPCR) is a noninvasive alternative to serum C-peptide measurement,[32] especially when the appropriate storage of blood samples (e.g. access to fridges and centrifuges) is limited. Indeed, when collected in boric acid, C-peptide in urine samples is stable at room temperature for 72 h.[33] It is used either in fasting or postprandial but, as previously mentioned, should not be used in cases of renal disease.[19] One of the first studies assessing its applicability demonstrated that 2 h UCPCR was as sensitive as plasma C-peptide measurement after a glucagon test in individuals with diabetes, under insulin therapy or not.[34] For insulin secretion assessment during an MTT, UCPCR at 120 min has also been shown to be an alternative to 90 min serum C-peptide in children with type 1 diabetes.[35] Importantly, UCPCR also helps to distinguish maturity-onset diabetes of the young (MODY) from type 1 diabetes,[36] although the diagnosis should be further confirmed by a genetic test.

6 | INSULIN RESISTANCE AND ITS ASSESSMENT

Different direct and indirect methods have been proposed and used for assessing insulin resistance. Choosing the appropriate index, either direct or indirect, should consider the aim of each particular study. For epidemiologic and research studies where insulin resistance is of primary interest, the hyperinsulinemic euglycemic clamp is usually used.[37] However, for assessing insulin sensitivity on a daily basis in clinical practice and under normal physiological conditions, indexes such as quantitative insulin sensitivity check index (QUICKI), HOMA-IR and Matsuda index are usually preferred.[38,39]

6.1 | Dynamic tests

Dynamic tests such as the hyperinsulinemic euglycemic clamp or the frequently sampled intravenous glucose tolerance test (FSIVGTT) are more complex and difficult to employ.

6.1.1 | Hyperinsulinemic euglycemic clamp

The hyperinsulinemic euglycemic clamp is the reference method for measuring insulin sensitivity/resistance.[40] This test requires a constant infusion of insulin and varying infusion of glucose to maintain euglycemia. Consequently, this is not a physiological test and is not the adequate method when the goal is to estimate insulin action and glucose dynamics under normal physiological conditions. As it requires intravenous insulin infusion and frequent blood sampling over a 2 h period, this procedure is operator-dependent, time-consuming, expensive and limited to people that can tolerate it.[41] Due to these disadvantages, other methods have been developed.

6.1.2 | Frequently sampled intravenous glucose tolerance test

Frequently sampled intravenous glucose tolerance test assesses insulin sensitivity by a computed mathematical analysis of glucose and insulin dynamics.[42] There were already some modifications to the original model, which consisted of an intravenously administered bolus of glucose, after which blood samples were frequently collected. The most common modification of FSIVGTT consists of a glucose bolus administration and an infusion of insulin 20 min after glucose injection.[43] Blood samples are collected frequently and periodically before and until 180 min after glucose infusion. Besides being an accurate technique for the measurement of insulin sensitivity in adults, adolescents and children,[44,45] FSIVGTT is also a useful tool for the identification of subtle, nonsymptomatic metabolic abnormalities even before the onset of type 2 diabetes.[44] Although easier to perform than a clamp, FSIVGTT is time-consuming, invasive and requires experienced personnel to perform it. Moreover, without the administration of insulin, it can fail in subjects with impaired glucose tolerance or T2D.[46]

6.2 | Indirect methods

The indirect and static methods for insulin resistance assessment such as HOMA-IR, QUICKI, Matsuda and insulin sensitivity index (ISI) (Table 1), are based on mathematical relations between plasma glucose, insulin and/or C-peptide. These methods have gained attention due to their lower complexity, lower cost and easy application. However, these methods also have advantages and disadvantages between them, such as ease of calculation and need for several timepoints from the OGTT/MTT (e.g. Matsuda index). In fact, the advantage of surrogates based on dynamic testing is that information about insulin secretion can be obtained at the same time as information about insulin action. However, if the main goal is to estimate insulin sensitivity/resistance, fasting surrogate indexes are preferable to dynamic ones as they are simpler

to obtain and do not require multiple timepoints of blood sampling.[47] Although indirect methods were mostly used in fundamental research, their application has been increasing both in clinical and epidemiological studies, as well as in clinical practice, due to the abovementioned advantages.

6.2.1 | Fasting insulin

The increase in fasting insulin levels indicates increased insulin resistance in a subject without diabetes. Thus, 1/fasting insulin can be used as an index on insulin sensitivity and will decrease as insulin resistance progresses.[48] However, and as previously mentioned, insulin levels are not normally distributed, so the correlation of this index with results from glucose clamp is not high. Moreover, this index should not be used in people with dysglycemia as it does not account for possible defects in insulin secretion.

6.2.2 | Fasting insulinogenic index

Insulinogenic index, the ratio of insulin to glucose in fasting, has also been proposed for assessing insulin sensitivity and predicts the development of T2D in some populations.[49,50] As expected, it correlates well with fasting insulin that can, in some situations, be used for assessing insulin sensitivity.[48] The opposite can also be calculated (i.e. glucose to insulin ratio) and insulin resistance will be assessed. However, in the case of people without diabetes, this ratio will be similar to 1/fasting insulin due to normoglycemia.[51] The glucose/insulin ratio has been especially used in cases of polycystic ovarian syndrome, which is characterized by insulin resistance.[52]

6.2.3 | HOMA-IR

Among the simple and indirect methods, HOMA-IR, based on glucose and insulin at fasting, is the best known and validated. HOMA was first described in 1985 as an easy calculation between insulin and glucose at fasting (Table 1).[22] This was later improved in 1998 to account for variations in hepatic and peripheral glucose resistance, rises in the insulin secretion curve for glycemia above 180 mg/dl and the contribution of circulating proinsulin and was named HOMA2-IR.[53] Due to all these variables, the latter is calculated through a computer model. Although HOMA2-IR is more accurate, HOMA-IR continues to be largely used as it does not require any specific software.[23] In fact, HOMA-IR has been used in numerous studies, not necessarily in the diabetes and obesity field, and either in dietary or physical activity interventions.[54–59] However, it may not be very accurate measuring insulin resistance once it uses fasting values and hyperinsulinemia generally results from a postprandial state.[60] Furthermore, HOMA-IR should not be used in individuals with poor glycemic control, marked β-cell dysfunction or under exogenous insulin treatment.[38] Also, it cannot be used when fasting glycemia is lower than 63 mg/dl (3.5 mmol/L).[22]

6.2.4 | Quantitative insulin sensitivity check index

Quantitative insulin sensitivity check index is based on fasting glucose and insulin, reflecting the balance between hepatic glucose production and insulin secretion maintained by the liver and pancreatic β-cells.[61] As insulin does not have a normal distribution, QUICKI takes advantage of a log transformation (Table 1). In this way, QUICKI has a linear correlation with the hyperinsulinemic euglycemic clamp, considered to be the gold standard method for assessing insulin action in vivo.[62] Indeed, QUICKI is very similar to HOMA-IR but the log transformation leads to QUICKI having the best correlation with the hyperinsulinemic euglycemic clamp, when compared to other indirect methods, such as HOMA-IR, HOMA2-IR and Matsuda index.[62–64]

Quantitative insulin sensitivity check index allows the prediction not only of changes in insulin sensitivity after therapeutic interventions but also the onset of diabetes.[65,66] Moreover, it performs better in insulin-resistant subjects,[62] being a good index to evaluate the progression of T2D. Indeed, it was already demonstrated that QUICKI is useful for following improvements in insulin sensitivity after dietary intervention and exercise in patients with T2D.[67] However, in sedentary individuals without diabetes, QUICKI did not properly detect changes in insulin sensitivity with exercise.[68] It was also not able to reflect changes in insulin sensitivity by obesity or growth hormone therapy.[69] Due to its calculation, QUICKI may become difficult to apply in subjects with severe diabetes to whom is not safe to withdraw the medication to perform the test.[62]

6.2.5 | Oral glucose insulin sensitivity

Oral glucose insulin sensitivity estimates insulin sensitivity during an OGTT, either of 2 or 3 h, and is the result of a mathematical model based on the dynamic relationship between insulin and glucose.[70] Although the calculation is not easy, it can be done using a spreadsheet. As

OGIS only requires blood sampling in three timepoints of the OGTT (0, 90 and 120 for a 2 h OGTT; 0, 120 and 180 min for a 3 h OGTT) and as it correlates with the results obtained with hyperinsulinemic euglycemic clamp,[70] OGIS is an attractive alternative for insulin sensitivity assessment. There are also studies using OGIS to assess insulin sensitivity during an MTT.[71,72] However, its accuracy in these cases is contradictory and thus still needs further validation.

6.2.6 | Matsuda index

Matsuda index evaluates whole-body insulin sensitivity and is calculated from plasma glucose and insulin concentrations in the fasting state and during OGTT (Table 1).[38] This index has the advantage of representing both hepatic and peripheral sensitivity to insulin.[38] Indeed, the fasting state values reflect hepatic insulin sensitivity whereas the values during the OGTT represent peripheral insulin sensitivity. Nonetheless, as it is calculated from blood samples taken before and during the OGTT, there is an uncomfortable need for successive blood sampling.[73] On the contrary, by using five timepoints, Matsuda becomes more accurate when compared to other surrogate indexes that use less timepoints.[47]

6.2.7 | Gutt index/Insulin sensitivity index ($ISI_{0,120}$)

The Gutt index is an ISI based on insulin and glucose values obtained at fasting and at 120 min of an OGTT (Table 1). It somehow replaced the use of another index, Cederholm index, that had a similar calculation but used not only fasting and 120 min timepoints, but also other timepoints of the OGTT, requiring more blood sampling.[74] Gutt index is well-correlated with direct estimates of insulin sensitivity obtained from the glucose clamp study,[75] across distinct glucose tolerance phenotypes and obesity. Moreover, in studies where several indexes derived from dynamic tests were compared, Gutt index was the best at foreseeing the onset of T2D.[63,76] However, this index is used only for assessing insulin sensitivity and does not have the ability of measuring insulin secretory capacity.[75]

6.2.8 | Duncan index/Fasting insulin resistance index

The Duncan index is an index of insulin resistance very similar to HOMA-IR, but the normalization factor is 25 instead of 22.5.[77] However, this index was never as used as HOMA-IR, and its use and value are not consensual within the scientific community.[78–80] However, it can be a valuable index, as the use of HOMA-IR is not recommended for fasting glycemia levels <63 mg/dl (<3.5 mmol/L) while Duncan index can be used in the entire range of glycemia.[63,77]

In summary, different studies highlight the importance of such indexes in the assessment of insulin resistance. Nonetheless, several limitations can still be highlighted when considering the usage of surrogate insulin resistance indexes: (i) lack of reproducibility observed in fasting insulin levels, which is due to its pulsatory secretion from the pancreas rather than with the indexes per se[60]; and (ii) lack of established and consensual intervals and cut-offs, as these vary too much between studies and populations.

Another drawback of surrogate indexes is the lack of reproducibility when measuring glucose and insulin, which comes from the unavoidable biological variability and from differences regarding the used analytical methodology.[61]

7 | INSULIN METABOLISM

Insulin clearance has recently been pointed out as an essential feature of glucose/insulin metabolism, as it has been hypothesized that its impairment could be related to an increased risk of developing T2D.[81,82]

It is well-known that immediately following release from the pancreatic β-cells, insulin enters the abdominal portal vein and then flows directly into the liver. In the postprandial state, about half of newly secreted insulin is taken up by hepatocytes on the first pass through the liver before entering extrahepatic circulation. Insulin that survives the first pass through the liver enters the hepatic veins and, thus, the systemic circulation where it can act on tissues. Finally, it is cleared by insulin-sensitive tissues including skeletal muscle, kidneys and liver (after recirculation). Circulating plasma insulin is thus determined by the balance between insulin release and clearance, which are both important parameters to establish plasma insulin levels. Insulin clearance can be estimated by direct or indirect methods. The term insulin clearance is used to describe the disappearance of insulin from the bloodstream in the entire organism, which can be conceptualized as the sum of two independent processes: hepatic clearance and extrahepatic clearance. Insulin clearance can be estimated by the ratio between C-peptide area under the curve (AUC) and insulin AUC along the OGTT.

7.1 | Disposition index

The DI is an integrating index between insulin secretion, resistance and metabolism. It is the product of insulin sensitivity and insulin secretory response and quantifies β-cell capacity to promote plasma glucose decline and, in a more complete index, integrates the insulin clearance. The feedback loop between insulin secretion and insulin sensitivity was first described as a hyperbolic curve by Bergman[83] and was further confirmed by Kahn and colleagues.[84] In the latter, the authors used the acute-insulin-response-to-glucose and the ISI obtained during the FSIVGTT. However, large clinical and epidemiologic studies mostly use data from the OGTT to calculate the DI. In prospective studies, DI calculated with the original formula decreases before the onset of diabetes, being a putative marker for inadequate β-cell compensation.[85]

Due to the difficulty of calculating DI, simpler surrogate indexes have been studied to infer DI, as is the case of IGI/fasting insulin, named oral disposition index (DI_O).[86] The latter was shown to be reliable in large-scale epidemiological studies with obese adolescents with normoglycemia, prediabetes and diabetes, where the use of FSIVGTT or OGTT is limited due to feasibility and cost.[87] However, in nondiabetic children, DI_O showed a modest correlation with DI.[88] Regarding the normoglycemic adult population, DI_O is predictive of diabetes onset over 10 years.[86]

8 | OTHER INDEXES/MEASURES FOR METABOLIC DISORDERS

Considering the importance of glycemic variability throughout a day lately time in range (TIR) has been addressed with great interest. Moreover, indexes considering other variables rather than glucose, insulin and C-peptide have been found to assess the risk of insulin resistance, T2D and metabolic syndrome. Indeed, indexes such as the HOMA-Adiponectin (HOMA-AD), visceral adiposity index (VAI), the lipid accumulation product (LAP) and the triglyceride-glucose index (TyG index) were shown to be suitable surrogates of insulin resistance in different pathological conditions such as diabetes, hypertension, cardiovascular disease, NAFLD and metabolic syndrome.[89–91]

8.1 | Time in range

With the increased use of CGMs devices, that have a sensor that measures interstitial glucose levels, other metrics of glycemic control have emerged. Although these include time above range and time below range, TIR has been the most used one (Figure 2). In diabetes, TIR refers to the amount of time in which a subject living with diabetes is within the target glucose range.[92] Conceptually, this range varies with each patient, and in theory, it approaches a more precise medicine intervention. For most patients, a TIR >70% is acceptable, for a range between 70 and 180 mg/dl (Figure 2).[93] TIR inversely correlates with HbA1c[94] and has been shown to predict the risk of long-term diabetes complications, such as retinopathy[95] and microalbuminuria.[95,96] Given the increasing use of CGMs, it is expected that the usage of metrics such as TIR also increases becoming an important tool for the management of the disease. Nevertheless, it is still far from the reality that one can know which mechanisms are affected (e.g. insulin secretion, metabolism and/or sensitivity) when TIR is not within the recommended values.

8.2 | HOMA-Adiponectin

HOMA-Adiponectin index was proposed based on a study in the Japanese population as an upgrade to HOMA-IR.[97] By adding adiponectin levels to the HOMA formula (see above), it indirectly adjusts to the individual degree of adiposity. However, there are studies that calculate this index with minor changes: some, including the original, replace the constant 22.5 by adiponectin levels, while other studies incorporate serum adiponectin levels in the denominator of the index. Probably due to the influence of adiposity, studies with obese individuals[98] show better performance and need of this index rather than studies in lean individuals,[99] where HOMA-AD does not have any clear advantage compared with HOMA-IR and even requires the measurement of adiponectin.

8.3 | Visceral adiposity index

Visceral adiposity index is a gender-specific indicator based on anthropometric measures (BMI and WC) and laboratory tests (triglycerides [TG] and high-density lipoprotein cholesterol [HDL-c]). It was firstly described in 2010 as a marker of visceral adipose function and insulin sensitivity.[100] Moreover, it is also associated with cardiometabolic risk.[100] In children and adolescents with obesity, VAI correlated with QUICKI and HOMA-IR and was shown to identify metabolic syndrome and was indicated as a powerful tool in the management of obesity together with dietary assessment.[101]

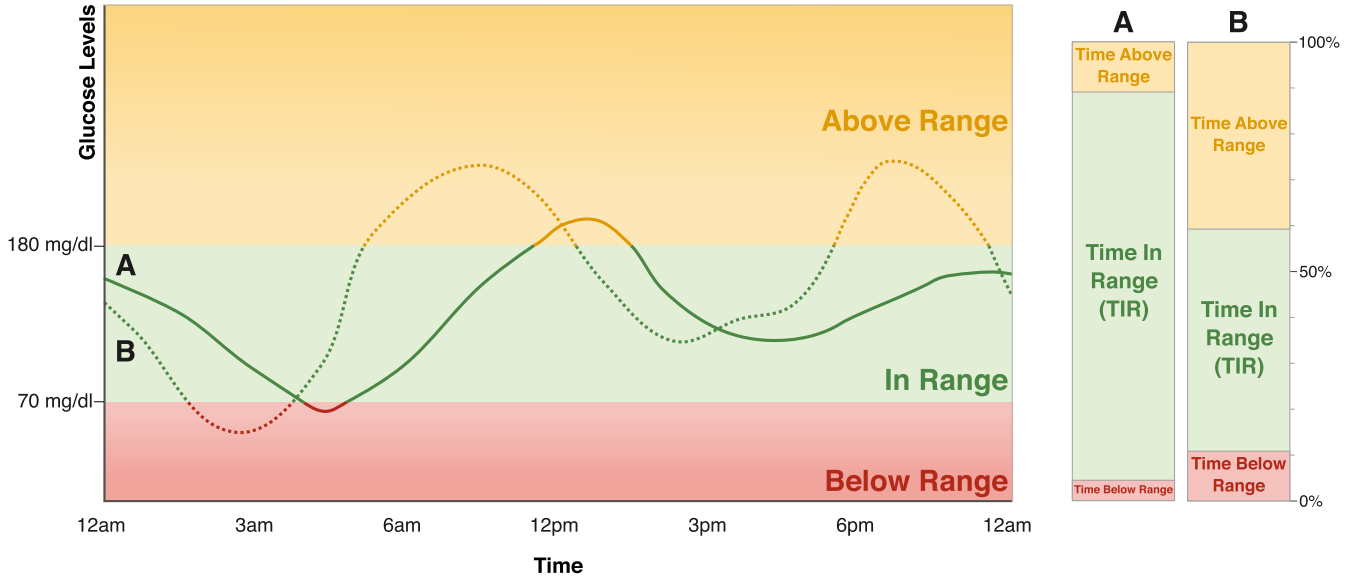

FIGURE 2 Time in range. Left—Representative images of two glucose levels profiles for 24 h (A and B). Right—Percentage of time that the A and B glucose levels profiles were above range (>180 mg/dl), in range (70 mg/dl ≤ x ≤ 180 mg/dl) or below range (<70 mg/dl). TIR, time in range.

8.4 | Lipid accumulation product

The LAP is also a gender-specific index based on WC and triglycerides[102–104] thus representing the anthropometric and physiological changes associated with excess lipid accumulation.[105] It has been demonstrated that LAP is a good predictor of metabolic syndrome[104] and that it provides a good distinction among individuals with prediabetes and diabetes.[89]

8.5 | TyG index

The TyG index is a simple, reliable and inexpensive tool to assess/predict body composition outcomes in response to dietary counselling.[90] Indeed, it revealed a potential to predict weight loss after energy restriction, with clear implications for personalized management of obesity in clinical and community settings.[106] Furthermore, TyG was sensitive to body fat changes after dietary intervention. On a nondiabetic population, TyG index and the TyG/HDL-C ratio had a moderate correlation with a direct method for assessing insulin-mediated glucose uptake, suggesting that these indexes are helpful for detecting subjects with insulin resistance when faced with the problems related to insulin measurement and action.[107]

The association between TyG index and liver fibrosis progression risk showed an increased TyG index that was found to be positively correlated with NAFLD fibrosis score and worsening of NAFLD severity. Additionally, higher serum levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase and HOMA-IR were observed in patients with higher quartiles of TyG index, while elevated TyG index was correlated with lower HDL-c serum concentrations.[91] Khamseh et al. proposed that TyG index and its related indexes including TyG-BMI and TyG-WC could identify NAFLD and liver fibrosis in overweight/obese subjects.[108,109] In a cross-sectional study, TyG index was exhibited to be the best test for screening simple steatosis and nonalcoholic steatohepatitis (NASH).[110] Additionally, TyG index was suggested as a steatosis biomarker that had an adequate diagnostic accuracy for the presence of steatosis.[111] The simplicity of calculation of the TyG index from two routine, low-cost biochemical measurements warrant further investigation of its role as an alternative evaluator of insulin resistance to improve the detection of subjects with high cardiometabolic risk and so facilitate the prevention of the development of chronic diseases associated with insulin resistance.

8.6 | Fatty liver index

The fatty liver index[112] (FLI) is a noninvasive and simple surrogate index of fatty liver. FLI is based on BMI, WC, triglycerides (TGs) and γ-glutamyltransferase. FLI is used to screen for hepatic steatosis, where FLI ≥60 rules in for hepatic steatosis, identifying subjects who should have lifestyle counselling and specialized care.[112] Studies have revealed FLI's utility in foreseeing the possibility of NAFLD in both healthy controls and insulin-resistant individuals with obesity.[112,113] Moreover, FLI has been shown to be useful for predicting the onset of T2D

during a 10-year period.[114] A higher FLI was also associated with T2D in several studies,[115–117] demonstrating once more a link between NAFLD and T2D and how valuable this index is as an early indicator of T2D risk. As FLI is a simple and affordable index, consecutive measures may be useful to assess dynamic changes in NAFLD.

8.7 | Fibrotic nonalcoholic steatohepatitis index

Although the first steps of NAFLD include simple steatosis, it can progress to NASH, which is characterized by inflammation and fibrosis, and even to hepatocellular carcinoma.[118,119] Therefore, it is of most relevance to address steatosis and fibrosis and detect NAFLD as soon as possible. Even though FIB-4 has been widely used in the last years for hepatic fibrosis, it does not perform well in a population with T2D.[120] Recently, Fibrotic nonalcoholic steatohepatitis index (FNI), an index that takes advantage of AST, HbA1c and HDL cholesterol was developed and validated as a tool to screen for fibrotic NASH.[121,122] Although recent, it was also already validated for people with diabetes and it is not affected by glycemic severity nor by T2D duration.[122] In both validation studies in people with metabolic diseases, FNI performed better than FIB-4.[120] FNI is thus an accurate, inexpensive and simple noninvasive score that can be used to screen for fibrotic NASH in both primary healthcare and diabetes-specialized settings.

A wide variety of methods are available for assessing metabolic control. However, when addressing patient metabolic control, several important factors need to be considered. We need mainly predictive indexes, that allow predicting how diabetes and its associated complications will progress in each individual and further technological advances that allow for better disease management.

9 | TECHNOLOGY DEVELOPMENT—TYPE 2 DIABETES

Technological development for the management of diabetes in home settings has been centered around glycemic control, with an overwhelming segment of the market being related to portable biosensing technologies for glucose determination. Indeed, it is expected that glucose monitoring will increase in the coming years, boosted not only by mature and established technologies, such as standard blood glucose meters (BGMs), but also advances in other portable devices, including CGMs.[123] BGMs and CGMs have been the focus of great advancements, both in industrial and academic sectors, aiming at improving their analytical sensing performance and patient opinion and experience throughout their use of such technologies, enhancing aspects such as noninvasiveness, connectivity and integration.[124] To do so, several routes have been taken, starting with investigating alternative biosensing schemes and transduction methods that can complement the gold standard glucose oxidase (GOx)-based, electrochemical sensors, using a range of new nanomaterials and recognition elements.[125,126] Alternatively, a major trend in the development of such CGMs has been the translation of technologies into fully wearable, noninvasive systems, that can harness chemical information from a range of different body fluids, such as sweat. A myriad of epidermal-worn systems have been put forward, improving on the minimally invasive, needle-based CGMs for interstitial fluid (IF) glucose detection, while opening the possibility to more dynamically study the fingerprints of glucose metabolism in these physiological fluids and its implication in diabetes.[127] Concurrently, CGM technologies have been used in integrated systems, including sensor-augmented insulin pumps, that can improve patient outcomes in glycemic control, in an attempt to reach artificial pancreas technologies using automated insulin delivery systems.[128] However, such devices still present some technological drawbacks, related to the physiology of glucose metabolism, that result in lag time regarding actual blood glucose levels measured by BGMs and the ones measured in target matrices of CGMs, mainly IF. As such, technological advancements that improve on this aspect are still needed, not only at the hardware level but also through predictive control software that can accurately estimate real blood glucose levels and trends for more accurate therapeutics,[129,130] using technologies such as deep learning and artificial intelligence (AI). Concurrently, the translation of technological knowledge for the development of biosensors and detection systems for the quantification of alternative biomarkers such as insulin, C-peptide or HbA1c has been a research focus.[131,132] With the possibility of measuring such biomarkers remotely at the point-of-care and outside the clinical setting, better adjustment of both short-term, glycemic control and long-term management of diabetes outcomes could be achieved. However, some technological barriers still need to be overcome, regarding the low circulating concentrations of some biomarkers and the more complex biosensing schemes that need to be implemented to accurately measure such metabolites, when compared to glucose detection. As such, if many or all of these aspects are included in comprehensive systems to be employed in homecare settings, it is expected that patient perception of diabetes technologies improves while encouraging the use of telemedicine principles in diabetes management, with the rise in digital diabetes technologies that implement all aspects of remote measurement,

data analysis and transmission to health providers and tailored therapeutics towards more personalized, precision diabetes management.

10 | DATA PROCESSING

One of the critical factors for the success of the technological approach presented above is the ability to collect and process patient data. Throughout this work, different metrics were mentioned to assess a patient's condition and deliver precise care and monitoring. All of this is possible by collecting patient data over time. In order words, the major data sources to infer a patient state are time series describing each metric. Data following this structure enable the prediction of future values of each metric, which can be used to alert a patient against unnoticed, harmful situations or simply inform the tendency of such values over the next hour. Currently, said tasks are easily handled by deep learning techniques such as temporal convolution networks[133] and auto encoders.[134]

However, these methods depend on regular sampled data at a fixed time interval, which cannot be guaranteed in a scenario where the patient is responsible for collecting the measurements. Thus, we need noise-robust methods, capable of handling missing and irregular sampled data over long periods of time. Fortunately, improvements regarding the training of Neural networks[135] spiked variations of already existing networks, robust to noise and capable of maintaining accuracy on irregular data, namely Liquid Time-constant networks[136] and Ordinary Differential Equation Long Short-Term Memory networks (ODE-LSTM).[137]

Data processing can be approached via two paradigms: batch and streaming. Batch processing can handle large amounts of data and deliver accurate and robust results. This is achieved by scheduling processing jobs capable of using large computational resources. An immediate downside of this approach is the slow delivery of results. Since processing jobs need to be scheduled, results are updated following those schedules and are not available immediately.

Contrary to batch processing, stream processing delivers results in near real time. This means that as fast as data comes in, results come out, providing fast responses. Nonetheless, the focus on fast delivery comes with some compromises with processing power: resources are limited to applying simpler tasks to incoming data. Such tasks include using simple forecast models and outlier detection, for instance.

Data processing platforms built upon the *lambda architecture* model[138] allow to combine both approaches, providing both sophisticated analytics based on big data and AI models and techniques, as well as fast delivery of simple, intuitive analytics and early warnings on potentially dangerous conditions being developed.

Finally, great concern must be placed on the privacy of patient data. Although the breakthroughs in healthcare enabled by data processing and AI are highly valuable, they cannot be achieved at the expense of patient privacy, especially from a regulatory perspective. The goal is to ensure that only certain players (including the patients and the accredited health professionals that take care of them) are able to associate a patient's identity with his/her data. As data are collected and processed by platform operators, they must ensure that such an identity association is always possible, while at the same time, neither they themselves nor any other third party has no means to do it on their own. This can be achieved through the concept of *data pseudonymization*, as provided under frameworks like the General Data Protection Regulation,[139] and its implementation in health-related scenarios is a major research challenge.

11 | PATIENT PERSPECTIVE—TYPE 2 DIABETES

The World Health Organization defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.[140] In diabetes this translates into considering the quality of life (QoL) of people living with diabetes as a key parameter in diabetes management.[141]

The QoL represents the ultimate objective of all treatment methodologies and health interventions. It can be measured by different tools and is considered as the status of the person's physical and mental well-being.[142] The main factors that impact positively the QoL are a good control of diabetes, which are also dependent on good self-management and the absence of diabetes-related complications. Also, the perceived ability of the people living with diabetes to control their own disease is a continuous learning process that results in an improved QoL.

We need also to consider that people living with a chronic illness live 24/7 with the disease and are the ones that take countless daily decisions regarding their treatment. This is a challenge for people living with diabetes because the demands are substantial.

Thus, all methods that allow a more efficient way of obtaining relevant information that can facilitate a better and easier management of diabetes are essential. Namely, the methods that people can use at home, at the point of care, in particular technologies that are not costly, complicated nor time-consuming.

The fact that there is no need to travel to the healthcare centres is also relevant for people with diabetes because it permits as well as a better use of their time. Besides the travelling, we need to consider the time spent at the healthcare centre. Self-management also requires remote control with a liaison with the healthcare practitioners. Mixed models of diabetes management are desirable, and they can be altered with time depending on the need of the patient. The possibility of both patients and healthcare practitioners to have access to the same information in real life allows a better management of the disease and QoL for the patient.

12 | FUTURE PERSPECTIVES AND CONCLUSIONS

Whereas glycemia will always be a key parameter for diabetes diagnosis and monitoring, there is an urgent need for an update in the way clinicians look at this complex disease.

There is an increasing awareness that each person is unique, and there is no such thing as one treatment fits all. Precision medicine proposes to consider individual differences in genetics, environment and lifestyle when considering disease prevention, presentation, diagnosis and treatment. Diabetes treatment is no longer glucocentric and apart from glucose management, there are other effective tools to slow the progression of the disease.

Evaluation of other biochemical parameters such as insulin, C-peptide and lipid profile is of utmost relevance for a better disease diagnosis and monitorization. Although these parameters are evaluated at diagnosis, there is still not an integrated overview of these, which individually are relevant but in combination can be much more informative and drive a more suitable clinical approach for each patient.

Usage and incorporation of the indexes referred throughout this review will certainly contribute to more precise and adequate therapeutics, greatly contributing to precision medicine.

One way of tackling this is the clustering approach,[7] which was designed to be more flexible, not providing definitive subphenotypes for individual patients in a clinical setting. This approach can be very useful for characterizing the metabolic heterogeneity prior to the clinical manifestation of T2D. The identification of subphenotypes suggests some potential therapeutic implications. The combined information from a few variables central to the development of diabetes is superior to the measurement of only one metabolite, glucose. By combining this information from diagnosis with information in the healthcare system this study[8] provides a first step towards a more precise, clinically useful, stratification, representing an important step towards precision medicine in diabetes.

Furthermore, it is now the perfect timing to implement a digital platform combining all the information given by simply measuring a few parameters (dealing properly with the privacy concerns mentioned above). In an era where people can easily access information in real time by using smartphones, it is enormous the potential for a platform where not only people with diabetes but also caretakers and healthcare practitioners would be able to easily access patient's information. In addition, these apps can be programmed not only to simply give information but to instruct people with diabetes, to help them better manage their disease.

The current literature highlights the importance of surrogate indexes of insulin resistance and insulin secretion for clinical and epidemiological studies. However, these are still not being used on a daily basis in clinical practice. Inclusion and usage of these surrogate indexes in clinical practice would allow not only better disease management but more appropriate and targeted pharmacotherapy. Still, in order to expand the usage of these indexes some practices should be implemented, namely, an easier and quicker way of measuring insulin and C-peptide. Alternatives to the currently used methods using less amount of biological samples and a system where the result could be assessed in much less time would allow measuring more than one parameter in real time.

An additional but crucial step would be the integration and analysis of all the gathered data. Once the person with diabetes is able to measure glucose, insulin and C-peptide or, in case of need, other parameters/indexes at home, sometimes more than once a day, this information needs to be transformed in a way that is accessible and understandable by the person with diabetes.

In long term, a platform like this could integrate all sorts of relevant information for the person with diabetes and for the healthcare practitioners, allowing a better and simpler disease management, more adequate therapeutics thereby reducing associated costs.

ACKNOWLEDGEMENTS

This work was supported by FEDER, Portugal2020, and co-financed by Lisboa2020 and Alentejo2020 (ALT20-03-0247-FEDER-113469 and LISBOA-01-0247-FEDER-113469), 'Fundação para a Ciência e a Tecnologia'—FCT iNOVA-4Health (UIDB/Multi/04462/2020), European Commission Marie Skłodowska-Curie Action H2020 (mtFOIE GRAS, grant agreement n. 734719) and the Sociedade Portuguesa de Diabetologia.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ORCID

Maria João Meneses https://orcid.org/0000-0002-8236-5411
Rita Susana Patarrão https://orcid.org/0000-0001-8701-2917
Tomás Pinheiro https://orcid.org/0000-0002-8346-4198
Inês Coelho https://orcid.org/0000-0003-2357-2477
Ana Carolina Marques https://orcid.org/0000-0001-6878-1040
João Nabais https://orcid.org/0000-0001-9572-6346
Elvira Fortunato https://orcid.org/0000-0002-4202-7047
João Filipe Raposo https://orcid.org/0000-0003-2589-7208
Maria Paula Macedo https://orcid.org/0000-0002-2549-0275

REFERENCES

1. Redondo MJ, Hagopian WA, Oram R, et al. The clinical consequences of heterogeneity within and between different diabetes types. *Diabetologia*. 2020;63(10):2040-2048.
2. Misra A, Garg S. HbA_{1c} and blood glucose for the diagnosis of diabetes. *Lancet*. 2011;378(9786):104-106.
3. Beck RW, Bergenstal RM, Laffel LM, Pickup JC. Advances in technology for management of type 1 diabetes. *Lancet*. 2019;394(10205):1265-1273.
4. Ribeiro RT, Andrade R, do Nascimento ÓD, Lopes AF, Raposo JF. Impact of blinded retrospective continuous glucose monitoring on clinical decision making and glycemic control in persons with type 2 diabetes on insulin therapy. *Nutr Metab Cardiovasc Dis*. 2021;31(4):1267-1275.
5. Banting FG, Best CH, Collip JB, et al. The effect produced on diabetes by extracts of pancreas. *Trans Assoc Am Physicians*. 1922;37:337-347.
6. Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. *J Clin Invest*. 1960;39:1157-1175.
7. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6(5):361-369.
8. Pina AF, Patarrao RS, Ribeiro RT, et al. Metabolic footprint, towards understanding type 2 diabetes beyond Glycemia. *J Clin Med*. 2020;9(8):2588.
9. Little RR, Wielgosz RI, Josephs R, et al. Implementing a reference measurement system for C-peptide: successes and lessons learned. *Clin Chem*. 2017;63(9):1447-1456.
10. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab*. 2008;294(1):E15-E26.
11. Fiorentino TV, Marini MA, Succurro E, Andreozzi F, Sesti G. Relationships of surrogate indexes of insulin resistance with insulin sensitivity assessed by euglycemic hyperinsulinemic clamp and subclinical vascular damage. *BMJ Open Diabetes Res Care*. 2019;7(1):e000911.
12. Bergman RN, Piccinini F, Kabir M, Kolka CM, Ader M. Hypothesis: role of reduced hepatic insulin clearance in the pathogenesis of type 2 diabetes. *Diabetes*. 2019;68(9):1709-1716.
13. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. *Cell*. 2015;163(5):1079-1094.
14. Fradkin JE, Hanlon MC, Rodgers GP. NIH precision medicine initiative: implications for diabetes research. *Diabetes Care*. 2016;39(7):1080-1084.
15. Rudvik A, Månsson M. Evaluation of surrogate measures of insulin sensitivity - correlation with gold standard is not enough. *BMC Med Res Methodol*. 2018;18(1):64.
16. Laurenti MC, Dalla Man C, Varghese RT, et al. Insulin pulse characteristics and insulin action in sdiabetic humans. *J Clin Endocrinol Metab*. 2021;106(6):1702-1709.
17. Jagannathan R, Neves JS, Dorcely B, et al. The Oral glucose tolerance test: 100 years later. *Diabetes Metab Syndr Obes*. 2020;13:3787-3805.
18. Wahren J, Larsson C. C-peptide: new findings and therapeutic possibilities. *Diabetes Res Clin Pract*. 2015;107(3):309-319.
19. Oram RA, Rawlingson A, Shields BM, et al. Urine C-peptide creatinine ratio can be used to assess insulin resistance and insulin production in people without diabetes: an observational study. *BMJ Open*. 2013;3(12):e003193.
20. Covic AMC, Schelling JR, Constantiner M, Iyengar SK, Sedor JR. Serum C-peptide concentrations poorly phenotype type 2 diabetic end-stage renal disease patients. *Kidney Int*. 2000;58(4):1742-1750.
21. Pacini G, Mari A. Methods for clinical assessment of insulin sensitivity and [beta]-cell function. *Best Pract Res Clin Endocrinol Metab*. 2003;17(3):305-322.
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419.
23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487-1495.
24. Hill NR, Levy JC, Matthews DR. Expansion of the homeostasis model assessment of beta-cell function and insulin resistance to enable clinical trial outcome modeling through the interactive adjustment of physiology and treatment effects: iHOMA2. *Diabetes Care*. 2013;36(8):2324-2330.
25. Pfützner A, Derwahl M, Jacob S, et al. Limitations of the HOMA-B score for assessment of beta-cell functionality in interventional trials-results from the PIOglim study. *Diabetes Technol Ther*. 2010;12(8):599-604.
26. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care*. 2008;31(10):1927-1932.
27. Lee EY, Hwang S, Lee SH, et al. Postprandial C-peptide to glucose ratio as a predictor of beta-cell function and its usefulness for staged management of type 2 diabetes. *J Diabetes Investig*. 2014;5(5):517-524.
28. Okuno Y, Komada H, Sakaguchi K, et al. Postprandial serum C-peptide to plasma glucose concentration ratio correlates with oral glucose tolerance test- and glucose clamp-based disposition indexes. *Metabolism*. 2013;62(10):1470-1476.
29. Saisho Y. Postprandial C-peptide to glucose ratio as a marker of beta cell function: implication for the management of type 2 diabetes. *Int J Mol Sci*. 2016;17(5):744.

30. Fujiwara D, Takahashi K, Suzuki T, et al. Postprandial serum C-peptide value is the optimal index to identify patients with non-obese type 2 diabetes who require multiple daily insulin injection: analysis of C-peptide values before and after short-term intensive insulin therapy. *J Diabetes Investig*. 2013;4(6):618-625.
31. Lee EY, Hwang S, Lee SH, et al. Postprandial C-peptide to glucose ratio as a predictor of β-cell function and its usefulness for staged management of type 2 diabetes. *J Diabetes Investig*. 2014;5(5):517-524.
32. Sasaki N, Miyamoto S, Niimi H, Nakajima H. C-peptide/creatinine ratio in early morning urine as an indicator of residual B-cell function in insulin-dependent diabetes. *Acta Paediatr Jpn*. 1991;33(3):375-380.
33. McDonald TJ, Knight BA, Shields BM, Bowman P, Salzmann MB, Hattersley AT. Stability and reproducibility of a single-sample urinary C-peptide/creatinine ratio and its correlation with 24-h urinary C-peptide. *Clin Chem*. 2009;55(11):2035-2039.
34. Koskinen P, Viikari J, Irjala K, Kaihola HL, Seppala P. Plasma and urinary C-peptide in the classification of adult diabetics. *Scand J Clin Lab Invest*. 1986;46(7):655-663.
35. Besser REJ, Ludvigsson J, Jones AG, et al. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. *Diabetes Care*. 2011;34(3):607-609.
36. Besser REJ, Shepherd MH, McDonald TJ, et al. Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-α/hepatocyte nuclear factor 4-α maturity-onset diabetes of the young from long-duration type 1 diabetes. *Diabetes Care*. 2011;34(2):286-291.
37. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237(3):E214-E223.
38. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. *Indian J Endocrinol Metab*. 2015;19(1):160-164.
39. Borai A, Livingstone C, Kaddam I, Ferns G. Selection of the appropriate method for the assessment of insulin resistance. *BMC Med Res Methodol*. 2011;11:158.
40. Shen SW, Reaven GM, Farquhar JW. Comparison of impedance to insulin-mediated glucose uptake in normal subjects and in subjects with latent diabetes. *J Clin Invest*. 1970;49(12):2151-2160.
41. Sharma VR, Matta ST, Haymond MW, Chung ST. Measuring insulin resistance in humans. *Horm Res Paediatr*. 2020;93(11–12):577-588.
42. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. *Am J Physiol Endocrinol Metab*. 1979;236(6):E667.
43. Saad MF, Anderson RL, Laws A, et al. A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance Insulin Resistance Atherosclerosis Study. *Diabetes*. 1994;43(9):1114-1121.
44. Cruz ML, Weigensberg MJ, Bergman RN, Goran MI. Frequency of hypoglycaemia during the intravenous glucose tolerance test in overweight children. *Int J Pediatr Obes*. 2007;2(2):122-125.
45. Conwell LS, Trost SG, Brown WJ, Batch JA. Indexes of insulin resistance and secretion in obese children and adolescents: a validation study. *Diabetes Care*. 2004;27(2):314-319.
46. Anderson RL, Hamman RF, Savage PJ, et al. Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests. The insulin resistance atherosclerosis study. *Am J Epidemiol*. 1995;142(7):724-732.
47. Altuve M, Severeyn E, Wong S. Adaptation of five indirect insulin sensitivity evaluation methods to three populations: metabolic syndrome, athletic and normal subjects. *Annu Int Conf IEEE Eng Med Biol Soc*. 2014;2014:4555-4558.
48. Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol*. 1993;137(9):959-965.
49. Kadowaki T, Miyake Y, Hagura R, et al. Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia*. 1984;26(1):44-49.
50. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. *Diabetes*. 1995;44(12):1386-1391.
51. Quon MJ. Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. *J Clin Endocrinol Metab*. 2001;86(10):4615-4617.
52. Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 1998;83(8):2694-2698.
53. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care*. 1998;21(12):2191-2192.
54. Boyer WR, Johnson TM, Fitzhugh EC, Richardson MR, Churilla JR. The associations between increasing degrees of HOMA-IR and measurements of adiposity among Euglycemic U.S adults. *Metab Syndr Relat Disord*. 2016;14(2):108-113.
55. Isokuortti E, Zhou Y, Peltonen M, et al. Use of HOMA-IR to diagnose non-alcoholic fatty liver disease: a population-based and inter-laboratory study. *Diabetologia*. 2017;60(10):1873-1882.
56. Lin CA, Liu YP, Chen YC, et al. Gender-specific and age-specific associations of the homoeostasis model assessment for IR (HOMA-IR) with albuminuria and renal function impairment: a retrospective cross-sectional study in Southeast China. *BMJ Open*. 2021;11(12):e053649.
57. Nakamura K, Sakurai M, Miura K, et al. HOMA-IR and the risk of hyperuricemia: a prospective study in non-diabetic Japanese men. *Diabetes Res Clin Pract*. 2014;106(1):154-160.
58. Paracha AI, Haroon ZH, Aamir M, Bibi A. Diagnostic accuracy of markers of insulin resistance (HOMA-IR) and insulin sensitivity (QUICKI) in gestational diabetes. *J Coll Physicians Surg Pak*. 2021;31(9):1015-1019.
59. Wang F, Han L, Hu D. Fasting insulin, insulin resistance and risk of hypertension in the general population: a meta-analysis. *Clin Chim Acta*. 2017;464:57-63.
60. DiNicolantonio JJ, Bhutani J, Jh OK, Crofts C. Postprandial insulin assay as the earliest biomarker for diagnosing prediabetes, type 2 diabetes and increased cardiovascular risk. *Open Heart*. 2017;4(2):e000656.
61. Placzkowska S, Pawlik-Sobecka L, Kokot I, Piwowar A. Indirect insulin resistance detection: current clinical trends and laboratory limitations. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2019;163(3):187-199.
62. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for

assessing insulin sensitivity In humans. *J Clin Endocrinol Metabol*. 2000;85(7):2402-2410.

63. Hanley AJ, Williams K, Gonzalez C, et al. Prediction of type 2 diabetes using simple measures of insulin resistance: combined results from the San Antonio heart study, the Mexico City diabetes study, and the insulin resistance atherosclerosis study. *Diabetes*. 2003;52(2):463-469.
64. Farkas GJ, Gordon PS, Trewick N, et al. Comparison of various indices in identifying insulin resistance and diabetes in chronic spinal cord injury. *J Clin Med*. 2021;10(23):5591.
65. Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. *Diabetes*. 2005;54(7):1914-1925.
66. Chen H, Sullivan G, Yue LQ, Katz A, Quon MJ. QUICKI is a useful index of insulin sensitivity in subjects with hypertension. *Am J Physiol Endocrinol Metab*. 2003;284(4):E804-E812.
67. Katsuki A, Sumida Y, Gabazza EC, et al. QUICKI is useful for following improvements in insulin sensitivity after therapy in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2002;87(6):2906-2908.
68. Duncan GE, Hutson AD, Stacpoole PW. QUICKI does not accurately reflect changes in insulin sensitivity with exercise training. *J Clin Endocrinol Metabol*. 2001;86(9):4115-4119.
69. Cutfield WS, Jefferies CA, Jackson WE, Robinson EM, Hofman PL. Evaluation of HOMA and QUICKI as measures of insulin sensitivity in prepubertal children. *Pediatr Diabetes*. 2003;4(3):119-125.
70. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabetes Care*. 2001;24(3):539-548.
71. Geloneze B, Lima MM, Pareja JC, Barreto MR, Magro DO. Association of insulin resistance and GLP-2 secretion in obesity: a pilot study. *Arq Bras Endocrinol Metabol*. 2013;57(8):632-635.
72. Brun JF, Ghanassia E, Fédou C, Bordenave S, Raynaud de Mauverger E, Mercier J. Assessment of insulin sensitivity (S I) and glucose effectiveness (S G) from a standardized hyperglucidic breakfast test in type 2 diabetics exhibiting various levels of insulin resistance. *Acta Diabetol*. 2013;50(2):143-153.
73. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;22(9):1462-1470.
74. Cederholm J, Wibell L. Insulin release and peripheral sensitivity at the oral glucose tolerance test. *Diabetes Res Clin Pract*. 1990;10(2):167-175.
75. Gutt M, Davis CL, Spitzer SB, et al. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. *Diabetes Res Clin Pract*. 2000;47(3):177-184.
76. Onishi Y, Hayashi T, Sato KK, et al. Comparison of twenty indices of insulin sensitivity in predicting type 2 diabetes in Japanese Americans: the Japanese American community diabetes study. *J Diabetes Complications*. 2020;34(12):107731.
77. Duncan MH, Singh BM, Wise PH, Carter G, Alaghband-Zadeh J. A simple measure of insulin resistance. *Lancet*. 1995;346(8967):120-121.
78. Del Prato S, Pozzilli P. FIRI: fasting or false insulin resistance index? *Lancet*. 1996;347(8994):132.
79. Gates JR, Parpia B, Campbell TC, Chen J. Evaluation of the FIRI (fasting insulin resistance index) and selected plasma parameters associated with insulin resistance as predictors of cardiovascular mortality in rural Chinese women. *Asia Pac J Clin Nutr*. 1997;6(3):200-202.
80. Cleland SJ, Petrie JR, Morris AD, Ueda S, Dorrian CA, Connell JM. FIRI: a fair insulin resistance index? *Lancet*. 1996;347(9003):770.
81. Duckworth WC, Bennett RG, Hamel FG. Insulin degradation: Progress and potential. *Endocr Rev*. 1998;19(5):608-624.
82. Bergman M, Abdul-Ghani M, DeFronzo RA, et al. Review of methods for detecting glycemic disorders. *Diabetes Res Clin Pract*. 2020;165:108233.
83. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest*. 1981;68(6):1456-1467.
84. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes*. 1993;42(11):1663-1672.
85. Xiang AH, Wang C, Peters RK, Trigo E, Kjos SL, Buchanan TA. Coordinate changes in plasma glucose and pancreatic β-cell function in Latino women at high risk for type 2 diabetes. *Diabetes*. 2006;55(4):1074-1079.
86. Utzschneider KM, Prigeon RL, Faulenbach MV, et al. Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care*. 2009;32(2):335-341.
87. Sjaarda LG, Bacha F, Lee S, Tfayli H, Andreatta E, Arslanian S. Oral disposition index in obese youth from normal to prediabetes to diabetes: relationship to clamp disposition index. *J Pediatr*. 2012;161(1):51-57.
88. Retnakaran R, Qi Y, Goran MI, Hamilton JK. Evaluation of proposed oral disposition index measures in relation to the actual disposition index. *Diabet Med*. 2009;26(12):1198-1203.
89. Ahn N, Baumeister SE, Amann U, et al. Visceral adiposity index (VAI), lipid accumulation product (LAP), and product of triglycerides and glucose (TyG) to discriminate prediabetes and diabetes. *Sci Rep*. 2019;9(1):9693.
90. Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord*. 2008;6(4):299-304.
91. Tutunchi H, Naeini F, Mobasseri M, Ostadrahimi A. Triglyceride glucose (TyG) index and the progression of liver fibrosis: a cross-sectional study. *Clin Nutr ESPEN*. 2021;44:483-487.
92. Wilmot EG, Lumb A, Hammond P, et al. Time in range: a best practice guide for UK diabetes healthcare professionals in the context of the COVID-19 global pandemic. *Diabet Med*. 2021;38(1):e14433.
93. Yapanis M, James S, Craig ME, O'Neal D, Ekinci EI. Complications of diabetes and metrics of glycemic management derived from continuous glucose monitoring. *J Clin Endocrinol Metab*. 2022;107(6):e2221-e2236.
94. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther*. 2019;21(2):81-85.
95. Lu J, Ma X, Zhou J, et al. Association of Time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care*. 2018;41(11):2370-2376.

96. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care*. 2019;42(3):400-405.
97. Matsuhisa M, Yamasaki Y, Emoto M, et al. A novel index of insulin resistance determined from the homeostasis model assessment index and adiponectin levels in Japanese subjects. *Diabetes Res Clin Pract*. 2007;77(1):151-154.
98. Makni E, Moalla W, Lac G, et al. The homeostasis model assessment-adiponectin (HOMA-AD) is the most sensitive predictor of insulin resistance in obese children. *Ann Endocrinol (Paris)*. 2012;73(1):26-33.
99. Michalczuk MT, Kappel CR, Birkhan O, Bragança AC, Álvares-da-Silva MR. HOMA-AD in assessing insulin resistance in lean noncirrhotic HCV outpatients. *Int J Hepatol*. 2012;2012:576584.
100. Amato MC, Giordano C, Galia M, et al. Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care*. 2010;33(4):920-922.
101. Vizzuso S, Del Torto A, Dilillo D, et al. Visceral adiposity index (VAI) in children and adolescents with obesity: No association with daily energy intake but promising tool to identify metabolic syndrome (MetS). *Nutrients*. 2021;13(2):413.
102. Wakabayashi I, Daimon T. A strong association between lipid accumulation product and diabetes mellitus in japanese women and men. *J Atheroscler Thromb*. 2014;21(3):282-288.
103. Mirmiran P, Bahadoran Z, Azizi F. Lipid accumulation product is associated with insulin resistance, lipid peroxidation, and systemic inflammation in type 2 diabetic patients. *Endocrinol Metab*. 2014;29(4):443-449.
104. Nascimento-Ferreira MV, Rendo-Urteaga T, Vilanova-Campelo RC, et al. The lipid accumulation product is a powerful tool to predict metabolic syndrome in undiagnosed Brazilian adults. *Clin Nutr*. 2017;36(6):1693-1700.
105. Xia C, Li R, Zhang S, et al. Lipid accumulation product is a powerful index for recognizing insulin resistance in non-diabetic individuals. *Eur J Clin Nutr*. 2012;66(9):1035-1038.
106. Vidal-Ostos F, Ramos-Lopez O, Blaak EE, Astrup A, Martinez JA. The triglyceride-glucose index as an adiposity marker and a predictor of fat loss induced by a low-calorie diet. *Eur J Clin Invest*. 2021;52:e13674.
107. Abbasi F, Reaven GM. Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: triglycerides × glucose versus triglyceride/high-density lipoprotein cholesterol. *Metabolism*. 2011;60(12):1673-1676.
108. Malek M, Khamseh ME, Chehrehgosha H, Nobarani S, Alaei-Shahmiri F. Triglyceride glucose-waist to height ratio: a novel and effective marker for identifying hepatic steatosis in individuals with type 2 diabetes mellitus. *Endocrine*. 2021;74:538-545.
109. Khamseh ME, Malek M, Abbasi R, Taheri H, Lahouti M, Alaei-Shahmiri F. Triglyceride glucose index and related parameters (triglyceride glucose-body mass index and triglyceride glucose-waist circumference) identify nonalcoholic fatty liver and liver fibrosis in individuals with overweight/obesity. *Metab Syndr Relat Disord*. 2021;19(3):167-173.
110. Simental-Mendía LE, Simental-Mendía E, Rodríguez-Hernández H, Rodríguez-Morán M, Guerrero-Romero F. The product of triglycerides and glucose as biomarker for screening simple steatosis and NASH in asymptomatic women. *Ann Hepatol*. 2016;15(5):715-720.
111. Fedchuk L, Nascimbeni F, Pais R, Charlotte F, Housset C, Ratziu V. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2014;40(10):1209-1222.
112. Bedogni G, Bellentani S, Miglioli L, et al. The fatty liver index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol*. 2006;6:33.
113. Cuthbertson DJ, Weickert MO, Lythgoe D, et al. External validation of the fatty liver index and lipid accumulation product indices, using 1H-magnetic resonance spectroscopy, to identify hepatic steatosis in healthy controls and obese, insulin-resistant individuals. *Eur J Endocrinol*. 2014;171(5):561-569.
114. Higashiura Y, Furuhashi M, Tanaka M, et al. High level of fatty liver index predicts new onset of diabetes mellitus during a 10-year period in healthy subjects. *Sci Rep*. 2021;11(1):12830.
115. Yadav D, Choi E, Ahn SV, et al. Fatty liver index as a simple predictor of incident diabetes from the KoGES-ARIRANG study. *Medicine*. 2016;95(31):e4447.
116. Franch-Nadal J, Caballeria L, Mata-Cases M, et al. Fatty liver index is a predictor of incident diabetes in patients with prediabetes: the PREDAPS study. *PLoS One*. 2018;13(6):e0198327.
117. Cuthbertson DJ, Koskinen J, Brown E, et al. Fatty liver index predicts incident risk of prediabetes, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). *Ann Med*. 2021;53(1):1257-1265.
118. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med*. 2018;24(7):908-922.
119. Meneses MJ, Silvestre R, Sousa-Lima I, Macedo MP. Paraoxonase-1 as a regulator of glucose and lipid homeostasis: impact on the onset and progression of metabolic disorders. *Int J Mol Sci*. 2019;20(16):4049.
120. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325.
121. Tavaglione F, Jamialahmadi O, De Vincentis A, et al. Development and validation of a score for fibrotic nonalcoholic steatohepatitis. *Clin Gastroenterol Hepatol*. 2022. In press.
122. Pina A, Meneses MJ, Ribeiro RT, Raposo JF, Macedo MP. Fibrosis nonalcoholic steatohepatitis index validation and applicability considering glycaemic severity and T2D duration. *Liver Int*. 2022;42(11):2577-2580.
123. Alcantara-Aragon V. Improving patient self-care using diabetes technologies. *Ther Adv Endocrinol Metab*. 2019;10:2042018 81882421.
124. Lee I, Probst D, Klonoff D, Sode K. Continuous glucose monitoring systems – current status and future perspectives of the flagship technologies in biosensor research. *Biosens Bioelectron*. 2021;181:113054.
125. Teymourian H, Barfidokht A, Wang J. Electrochemical glucose sensors in diabetes management: an updated review (2010–2020). *Chem Soc Rev*. 2020;49(21):7671-7709.
126. Sehit E, Altintas Z. Significance of nanomaterials in electrochemical glucose sensors: an updated review (2016-2020). *Biosens Bioelectron*. 2020;159:112165.
127. Kim J, Campbell AS, Wang J. Wearable non-invasive epidermal glucose sensors: a review. *Talanta*. 2018;177:163-170.
128. Marks BE, Williams KM, Sherwood JS, Putman MS. Practical aspects of diabetes technology use: continuous glucose

monitors, insulin pumps, and automated insulin delivery systems. *J Clin Transl Endocrinol*. 2022;27:100282.
129. Sanai F, Sahid AS, Huvanandana J, et al. Evaluation of a continuous blood glucose monitor: a novel and non-invasive wearable using bioimpedance technology. *J Diabetes Sci Technol*. 2021;193229682110541.
130. Li K, Liu C, Zhu T, Herrero P, Georgiou P. GluNet: a deep learning framework for accurate glucose forecasting. *IEEE J Biomed Health Inform*. 2020;24(2):414-423.
131. Soffe R, Nock V, Chase JG. Towards point-of-care insulin detection. *ACS Sensors*. 2019;4(1):3-19.
132. Pohanka M. Glycated hemoglobin and methods for its point of care testing. *Biosensors*. 2021;11(3):70.
133. Bai S, Kolter JZ, Koltun V. An empirical evaluation of generic convolutional and recurrent networks for sequence modeling. *arXiv preprint arXiv:180301271*. 2018.
134. Pang G, Shen C, Cao L, Hengel AVD. Deep learning for anomaly detection: a review. *ACM Comput Surv*. 2021;54(2):38.
135. Chen RT, Rubanova Y, Bettencourt J, Duvenaud DK. Neural ordinary differential equations. *Adv Neural Inf Process Syst*. 2018;31:6571-6583.
136. Hasani R, Lechner M, Amini A, Rus D, Grosu R. Liquid time-constant networks. Paper Presented at: Proceedings of the AAAI Conference on Artificial Intelligence. 2021.
137. Lechner M, Hasani R. Learning long-term dependencies in irregularly-sampled time series. *arXiv preprint arXiv:200604418*. 2020.
138. Warren J, Marz N. *Big Data: Principles and Best Practices of Scalable Realtime Data Systems*. Simon and Schuster; 2015.
139. Regulation P. Regulation (EU) 2016/679 of the European Parliament and of the council. *Regulation* (*eu*). 2016;679:2016.
140. World Health Organization. Constitution of the World Health Organization.
141. Rubin RR, Peyrot M. Quality of life and diabetes. *Diabetes Metab Res Rev*. 1999;15(3):205-218.
142. Palamenghi L, Carlucci MM, Graffigna G. Measuring the quality of life in diabetic patients: a scoping review. *J Diabetes Res*. 2020;2020:5419298.
143. Tura A, Kautzky-Willer A, Pacini G. Insulinogenic indices from insulin and C-peptide: comparison of beta-cell function from OGTT and IVGTT. *Diabetes Res Clin Pract*. 2006;72(3):298-301.
144. Saisho Y, Kou K, Tanaka K, et al. Postprandial serum C-peptide to plasma glucose ratio as a predictor of subsequent insulin treatment in patients with type 2 diabetes. *Endocr J*. 2011;58(4):315-322.
145. Piccinini F, Bergman RN. The measurement of insulin clearance. *Diabetes Care*. 2020;43(9):2296-2302.

How to cite this article: Meneses MJ, Patarrão RS, Pinheiro T, et al. Leveraging the future of diagnosis and management of diabetes: From old indexes to new technologies. *Eur J Clin Invest*. 2022;00:e13934. doi:10.1111/eci.13934