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"Mild dysglycemia" in type 2 diabetes: to be neglected or not?

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ABSTRACT

"Mild dysglycemia" in type 2 diabetes can be defined by the range of HbA1c levels ≥ 6.5% (48 mmol/mol) and < 7% (53 mmol/mol), which corresponds to when the risk for vascular complications begins to increase. This "mild dysglycemia" is characterized by both a dawn phenomenon (a spontaneous blood glucose rise in the early morning) and an excess of post-prandial glucose excursions in the absence of abnormal elevation in basal glucose, especially during nocturnal periods. This represents an intermediary stage between pre-diabetes (HbA1c ≥ 5.7%, 39 mmol/mol, and < 6.5%, 48 mmol/mol) and those who begin to show a steadily progressive worsening in basal glucose (HbA1c ≥ 7%, 53 mmol/mol). Should this relatively minor intermediate dysglycemic phase deserve more attention, that is the question. The now available incretin-based therapies, and more specifically the DPP-4 inhibitors provide the clinician with the possibility to reduce or eradicate both the dawn phenomenon and post-meal glucose excursions with minimal side effects. The availability of 24-h glycemic profiles in those with "mild dysglycemia" will help to describe their individual glycemic phenotype, based on which the early and appropriate life style changes and/or pharmacological interventions can be introduced.

Type 2 diabetes is a syndrome characterized by progressive and relentless deterioration in glucose homeostasis (Monnier, Colette, Dunseath, & Owens, 2007; UK Prospective Diabetes Study Group 16, 1995) necessitating that treatment be adjusted along the diabetes continuum (Inzucchi et al., 2012). Currently, most national and international organizations recommend that an HbA1c < 7% (53 mmol/mol) be the glycemic target in most adult persons with type 2 diabetes (American Diabetes Association (ADA) (American Diabetes Association, 2014a), European Association for the Study of Diabetes (EASD) (Inzucchi et al., 2012) and the International Diabetes Federation (IDF) (IDF 2012 Clinical Guidelines Task Force, 2012)). However, it is also recommended that this threshold be modulated on an individual basis (IDF 2012 Clinical Guidelines Task Force, 2012; Inzucchi et al., 2012). In 2008, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008) demonstrated that striving to achieve too stringent glycemic goals (HbA1c < 6%, 42 mmol/mol) with intensive therapy resulted in increased frequency of hypoglycemia and independently increased cardiovascular related mortality (Bonds et al., 2009; Zoungas et al., 2010). This is of particular relevance for certain groups of patients such as the elderly and those with long term poor glycemic control with pre-existing cardiovascular disease or who are at high risk of cardiovascular disease (Cryer, 2014). The Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) (Zoungas et al., 2010) study and a post hoc analysis of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) datasets (Melbin et al., 2013) indicated that severe hypoglycemic episodes were associated with more cardiovascular deaths or acute cardiac dysrhythmia than observed with minor hypoglycemia. Exposure to hypoglycemia, especially episodes of severe hypoglycemia, should therefore be avoided. Consequently, most recommendations propose that the HbA1c target should be greater than 7% (53 mmol/mol) in those who have an elevated risk for cardiovascular disease (Cryer, 2014; IDF 2012 Clinical Guidelines Task Force, 2012; The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008) whereas the threshold should be 6.5% (48 mmol/mol) in those with a shorter disease duration, no established cardiovascular complications and a low risk of hypoglycemia (IDF 2012 Clinical Guidelines Task Force, 2012; Inzucchi et al., 2012). The rationale for this lower HbA1c target is based on the fact that both the DETECT-2 epidemiological study (Colagiuri et al., 2011) and the interventional ADVANCE trial (Zoungas et al., 2012) have demonstrated that the prevalence of retinopathy and other microvascular complications remains low at HbA1c levels < 6.5% (48 mmol/mol), but thereafter steadily increases throughout HbA1c worsening. Therefore, recently diabetes mellitus has been re-defined to include all individuals with an HbA1c level ≥ 6.5% (48 mmol/mol) (American Diabetes

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Association, 2014b). Combined with the knowledge that the risk of microvascular complications increases beyond this value, should we therefore not highlight the potential benefit of intervention in those with "mild dysglycemia" (HbA1c between 6.5 and 7%)?

1. The key stages in the evolution of type 2 diabetes

The features of dysglycemia in persons with type 2 diabetes can be divided into the following components: (1) basal hyperglycemia, (2) post-prandial hyperglycemia (Monnier et al., 2007, 2003; Monnier, Lapinski, & Colette, 2003; Monnier, Colette, & Owens, 2011) and (3) the dawn phenomenon (Bolli & Gerich, 1984; Carroll & Schade, 2005; Monnier, Colette, Dejager, & Owens, 2013). These aforementioned glycemic abnormalities do not occur simultaneously in the evolution of type 2 diabetes but vary in their contribution throughout the natural history of the disease (Fig. 1).

1.1. The dawn phenomenon

The term "dawn phenomenon" was introduced in 1981 by Schmidt, Hadji-Georgopoulos, Rendell, Margolis, and Kowarski (1981) in relationship to type 1 diabetes. Soon thereafter, it became obvious that this phenomenon corresponds to a rise in plasma glucose and/or insulin requirements during the end of the nocturnal period, in the absence of any carbohydrate intake. The dawn phenomenon is mainly due to the circadian variation in hepatic glucose production, which starts to increase in the evening and reaches a maximum towards the end of an overnight fast and then declines during daytime until its late afternoon nadir (Boden, Chen, & Urbain, 1996). The two main consequences of the rise in circulating blood glucose overnight include elevation of the early morning fasting blood glucose and secondly abnormally high and delayed post-breakfast glucose excursions referred to as the "extended dawn phenomenon" (Monnier et al., 2007). This latter phenomenon is postulated to be due to the combined influence of an extended overproduction of glucose by the liver and intestinal hydrolysis of carbohydrates from the breakfast, which contributes to the overall hyperglycemia. Both phenomena, and more specifically the dawn phenomenon, are not encountered in non-diabetic subjects (Porcelatti, Lucidi, Bolli, & Fanelli, 2013) since the hepatic glucose output in the early morning is counteracted by an increase in the endogenous insulin secretion (De Feo et al., 1986).

We have recently demonstrated (Monnier, Colette, Dejager, & Owens, 2014), that the "dawn phenomenon" was present in a group of 50 well-controlled persons with type 2 diabetes with a HbA1c ranging from 5.7% (39 mmol/mol) to 6.5% (48 mmol/mol), predominantly treated with dietary measures alone (34 out of 50, 68%). In contrast, the mean post-prandial glucose (131 mg/dl, 7.3 mmol/l) and overall 24 hours mean glucose level (115 mg/dl, 6.4 mmol/l) were both within the normal range in most of the participants (Fig. 2). This observation therefore suggests that the dawn phenomenon represents the earliest expression of dysglycemia in the natural history of type 2 diabetes (Fig. 1).

1.2. Post-meal hyperglycemia

In 2003 we demonstrated that post-prandial hyperglycemia made the major contribution to the overall hyperglycemia (70%) in persons with type 2 diabetes treated with oral anti-diabetic agents (Monnier et al., 2003). In 2007 this finding was confirmed by analyzing 24-h continuous glucose profiles of non-insulin-treated persons with type 2 diabetes at different levels of HbA1c (Monnier et al., 2007). As soon as HbA1c levels exceeded 6.5% (48 mmol/mol), we observed an abnormal elevation of post-meal glucose levels despite pre-breakfast glucose levels within the normal range, provided the HbA1c remained below 7% (53 mmol/mol). This deterioration, which precedes that of basal hyperglycemia, has been recently reconfirmed (Monnier et al., 2014) (Fig. 2). We examined 100 persons with type 2 diabetes (HbA1c < 7%, 53 mmol/mol), treated either with dietary measures alone or in combination with oral anti-diabetic agents. The differences between those exhibiting "mild dysglycemia" (HbA1c 6.5–6.9%, 48–52 mmol/mol, n = 50) compared with those with even better glycemic control (HbA1c < 6.5%, 48 mmol/mol, n = 50) was due to the greater post-meal excursions in the former group (Monnier et al., 2014). Less of a quarter of those with an HbA1c < 6.5% (48 mmol/mol), had an average two-hour post-meal glucose (mean of post-breakfast, post-lunch and post-dinner values) above the upper limit of normal of 140 mg/dl (7.8 mmol/L). In contrast, more than one half of those with an HbA1c level between 6.5% (48 mmol/mol) and 6.9% (52 mmol/mol) exceeded this threshold value (Monnier et al., 2014). Therefore, persons with an HbA1c ≥ 6.5% (48 mmol/mol) but < 7% (53 mmol/mol), i.e. with "mild dysglycemia", differ pathophysiologically from those with an HbA1c < 6.5% (48 mmol/mol) by virtue of both the greater magnitude and frequency of post-meal glucose excursions in the former group. The "dawn phenomenon" was present in both groups whereas basal hyperglycemia was absent. Therefore, one can conclude that excess post-prandial hyperglycemia is the second abnormality in the natural history of most persons with type 2 diabetes, while remaining with an HbA1c level below 7% (53 mmol/mol) (Fig. 1).

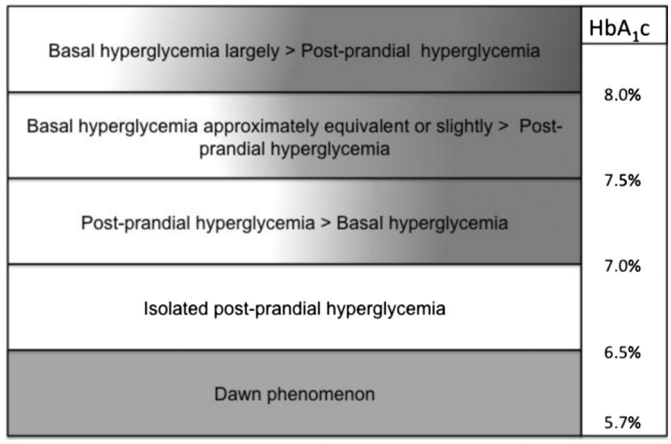

Fig. 1. Respective contributions of the 3 main glycemic disorders (dawn phenomenon, basal and post-prandial hyperglycemia) to the dysglycemia of type 2 diabetes mellitus across the HbA1c spectrum.

A significant percentage of the participants (48%) with an HbA1c ≥ 6.5% (48 mmol/mol) but < 7% (53 mmol/mol) did not however exhibit an average post-meal glucose level above 7.8 mmol/l, a threshold which is rarely enforced to define normality (Polonsky, Given, & Van, 1988). Such an observation therefore indicates that, in persons with diabetes mellitus, there exist large inter-individual variations in blood glucose patterns (Bergenstal et al., 2013). The state of "mild dysglycemia" in those with type 2 diabetes does not escape from this general observation. Consequently, even though HbA1c is acknowledged to be a key glycemic marker for estimating the risk of diabetic complications, it remains that HbA1c by itself does not provide sufficient information for fine-tuning of glycemic control at an individual level. An expert panel of diabetes specialists chaired by Richard Bergenstal (2013) recently recommended that the clinical decision making process in the management of persons with type 1 diabetes should be based not only on HbA1c but also on the assessment of ambulatory glucose profiles by using either discontinuous self monitoring of blood glucose (SMBG) or preferentially continuous subcutaneous glucose monitoring (CGM). Intermittent CGM in parallel to a structured SMBG (Polonsky et al., 2011) may be also of value to persons with type 2 diabetes in an attempt to capture the post-meal peaks, which is rarely attained even with multiple-point SMBG. Utilizing CGM in type 2 diabetes has resulted in re-setting the timing for optimal estimating of the post-

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