Postprandial glycemia: review of current pathophysiological, epidemiological and clinical aspects

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Abstract: One of the most difficult current medical problems is the growing epidemics of diabetes mellitus. The contemporary treatment aims are not only to secure the patients survival and to protect them from the acute symptoms but also to avoid the occurence of the chronic complications of the disease. This paper contains a review of the role that postprandial hyperglycemia plays in the treatment of diabetes mellitus especially type 2. The authors summarize the findings of patophysiological and epidemiological macroangiopathy studies that indicate the use of prandial glucose regulation in clinical practice. This review contains discussion on the postulated mechanism in which short-lasting increases in plasma glucose concentration can damage vessel wall leading to atherosclerosis. Epidemiological studies showing the strong correlation between postprandial (and post-challenge) plasma glucose levels with cardiovascular endpoints are also discussed. Moreover, in this paper the reader may find a discussion on practical aspects of postprandial hyperglycemia monitoring in the treatment of diabetic patient, focusing on the relationship between prandial glycaemia and long term glycaemia control expressed by HbA_{1c} measurements. The guidelines for monitoring postprandial glycaemia are also included. The modern therapeutic possibilities aiming at post-prandial hyperglycaemia are also showed.

Key words: complications, diabetes, postprandial glycaemia

INTRODUCTION

Up-to-date treatment of diabetes of type 1 and type 2 requires therapeutic intervention which not only allows to survive and avoid acute symptoms, but also prevents developing late complications. The cost of diabetes treatment represents a significant financial burden for every developed country budget with predominant costs of chronic complications treatment. It is a well-known fact that late complications of diabetes develop as a consequence of an insufficient glucose blood level compensation. The basic parameter used in evaluation of the metabolic balance is a proportion of glycosylated hemoglobin (HbA_{1c}). The parameter most appropriately correlates with the mean glycemia level during the last three months. The majority of the guidelines suggest HbA_{1c} monitoring twice a year, so the only advantage is a possibility to evaluate success or failure of the therapy, with no usefulness in adaptation of treatment to the unstable glucose blood level. A proportion of HbA_{1c} is linked with the mean glucose blood level and does not reflect a diurnal glycemia fluctuation. Monnier et al. presented a percentage of fasting and postprandial glycemia depending on HbA_{1c} in a large group of patients with type 2 diabetes. Fasting glycemia turned out to be crucial in the worst controlled patients. The diurnal glycemia predominates when HbA_{1c} is lower than 8.5% [1]. The postprandial period includes several hours after a meal when the glucose concentration reaches the highest value in 24 hours. The glucose blood level evaluation is not performed in that period and the treatment is not adjusted to this value. However there is a large body of evidence indicating that even a relatively short-lasting high postprandial glucose level may influence the development of particularly microangiopathic complications, regardless of the overall glucose balance estimated by HbA_{1c}.

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In this review the authors discuss pathophysiology, epidemiology and clinical aspects concerning reciprocal relationship of postprandial glycemia (PPG) and atherosclerosis and ischemic heart disease development.

The β cell disorder and pathophysiology of postprandial period

Adequate insulin secretion by β cells ensures the maintenance of glucose level in a normal range. That precise mechanism fails in millions of patients resulting in diabetes development. In type 1 diabetes the absolute insulin baseline and postprandial deficiency is observed. The majority of cases had type 2 diabetes. In the pathogenesis the two main defects such as impairment of insulin secretion and reduced insulin sensitivity have been observed. The cases of type 2 diabetes are of a wide range: from insulin resistance predominance coexisting with relative insulin deficiency to predominant secretion defect with slight insulin resistance.

There are some significant questions concerning impairment of insulin secretion in type 2 diabetes. What is a share of the β cell disorder and insulin resistance in pathophysiology of type 2 diabetes in consecutive stages of the disease? Does impairment of insulin secretion is a consequence of loss of cell mass or of the β cell disorder? In clinical practice the diabetes type 2 is of multifactorial origin. The impairment of insulin secretion with concomitant insulin resistance forms the clinical picture of the disease development (fig.).

In the first stage of type 2 diabetes increasing insulin resistance is accompanied by increase of insulin secretion. As long as the β cell compensation mechanism remains efficient the glucose level stays normal. On a certain disease period the β cell disorder begins to escalate and the diabetes starts to manifest itself clinically. It is worth mentioning that some important trials in patients with type 2 diabetes (int. al. the United Kingdom Prospective Diabetes Study) showed intensifying insulin secretion impairment and stable insulin resistance in a fully developed disease [2,3].

Impairment of insulin secretion in diabetes type 2 patients can be demonstrated in several ways. The very early disorder which reveals in the beginning of the disease is the first phase insulin secretion decline indicated by the intravenous glucose tolerance test (IVGTT). In the later disease phase delayed and decreased insulin secretion in the late secretion phase after glucose load in the oral glucose tolerance test (OGTT) or after a composed meal is observed. In a very advanced phase of the disease the insulin secretion remains at a very low baseline level [4].

It is worth mentioning that in type 2 diabetes impairment of the normal glucose oscillation is observed [5]. It becomes irregular and of low amplitude. A decrease of the proportion of insulin in a cell secretion product (with increase in proinsulin) is noted [5]. Incretin secretion is also impaired [6].

Considering the decrease of insulin secretion the question should be raised - to what degree it depends on reduced β cell mass and to what degree on its impaired function. It seems that the two phenomena coexist and they are both essential for the disease development. In the autopsies of the diabetic patients and in animal models the 30–50% decrease of the β cell number and amyloid accumulation is observed [6-8]. However, that does not explain increased damage. Impairment of those β cells which survived the initial disease phase is equally important. Several lines of evidence showed multifunctional impairment of β cells, and importantly, the phenomenon is partially reversible [9].

Hyperglycemia is essential in the etiology of micro- and macroangiopathies. In the recent years the toxicity of major diurnal glucose level fluctuation as well as the unfavorable influence of excessive postprandial glucose level increase have been emphasized [9]. The postprandial glycemia level depends on many factors such as pre-prandial glycemia, kind of food and carbohydrates content, stomach motor activity, efficiency of neurohormonal system and incretin secretion, mainly a peptide-inhibitor of gastric secretion, secretin, cholecystokinin, gastrin and glucagon-like peptide-1. For the postprandial glycemia the normal initial phase of insulin secretion after an alimentary stimulus, glucagon concentration and uptake, and metabolism of glucose in the liver and peripheral tissue are of great importance. Carbohydrate and lipid metabolisms are closely associated and decide on the energetic balance of the body. During the development of diabetes this mechanism is unsettled, which results in postprandial hyperglycemia and hyperlipidemia [9].

Food is the main and natural source of energy. Carbohydrates, lipids and proteins are the basic nutritive substances which, after being digested in gastrointestinal tract, are absorbed in blood or lymph. The resorption follows the food uptake with the lasting time depending mainly on the content and type of carbohydrates and lipids in a meal. After a carbohydrates-rich meal the resorption period comes to 2–3 hours, after a mixed meal 3–5 hours, and after a lipid-rich meal - 8–10 hours [10,11].

Glucose or lipid excess is a very unfavorable phenomenon leading to impaired interaction between inflammatory response cells and endothelium [12]. It is shown that postprandial hyperglycemia and free fatty acids increase are accompanied by inflammatory reaction and oxidative stress [13,14]. The sources of increased reactive oxygen species (ROS) production in hyperglycemia and hyperlipidemia are glycolytic pathway and β-oxydation of fatty acids in endothelial cells [12]. The main sources of ROS represent stimulated neutrophils. In diabetic patients these cells reveal subliminal activation and release the excess of peroxide anions and hydrogen peroxide in a resting state [15]. It was proved that the neutrophil ROS release increases with postprandial hyperglycemia [16]. The oxidation stress in diabetic patients is a result of increased ROS production as well as insufficient oxidation mechanisms. The main role in this regulation is attributed to superoxide dismutase (SOD), catalase and gluthation complex (reduced glutation, peroxidase, glutation reductase). In diabetic pa-

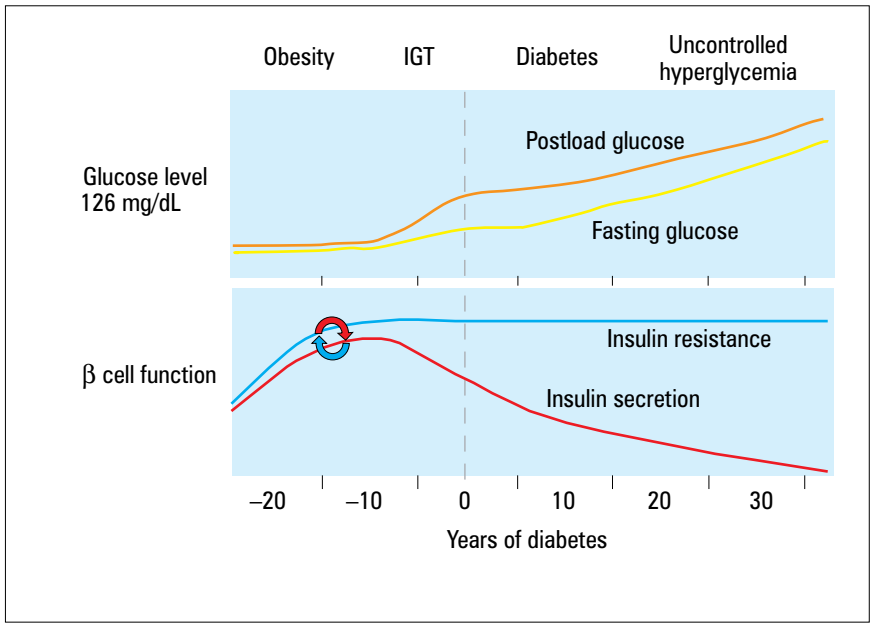

Fig. Reciprocal relationship of 2 main pathophysiologic defects in natural history of diabetes type 2 (according to the International Diabetes Center [IDC]. Minneapolis, Minnesota). IGT – impaired glucose tolerance

tients, even if well metabolically controlled, the SOD activation and the glutation bioavailability decrease were observed [17]. It was proved that enhancement of postprandial oxidative stress depends on the kind of food. Highly caloric foods rich in carbohydrates with high glycemic index and saturated fatty acids seem to be the most unfavorable and toxic for endothelium [14]. Increased ROS production is linked with protein kinase C, active forms of nicotinamide adenine dinucleotide phosphate (NAD(P)H) and nuclear transcription factor kappa B activation [12,13,18]. These molecules play a key role in the inflammatory state cascade, which is essential in diabetes and in micro- and macroangiopathic chronic complications [19].

Pathophysiologically, the reduction of glucose level increase as well as the postprandial glucose level reduction seem to be reasonable.

Postprandial glycemia and cardiovascular complications

In 1997 the American Diabetes Association (ADA) and World Health Organization (WHO) modified the diagnostic criteria for diabetes by decreasing the normal lower border of fasting glucose level from 140 to 126 mg%. Moreover, the new term, i.e. impaired fasting glucose (IFG) was accepted and the WHO indicated the necessity of supporting the OGTT in doubtful cases:

1) fasting plasma glucose (FPG) between 110–125 mg/dl,
2) elderly patients with normal weight, a high risk of diabetes and normal FPG [20, 21].

After the new criteria were published a debate started about the relation between fasting glucose level and postprandial glycemia in the identification of diabtes in a high-risk population. The most important issue is how fasting and postprandial hyperglycemia determine the patient's general condition and death risk. The issue was analyzed in the DECODE trial [22].

The analyzed data lead to the conclusion that when the glucose intolerance diagnosis was based on the fasting glucose level, patients with previously diagnosed diabetes were in the worse prognosis group than those who were newly diagnosed. If the only disorder was the elevated fasting glucose level the prognosis was similar to those with no glucose tolerance disorder. For a change, if the glucose tolerance disorder diagnosis was based on the 2-hour postprandial blood glucose test, prognoses on survival of patients were worse in both groups. Moreover, 31% of patients with diabetes diagnosed by the 2-hour postprandial blood glucose test had normal fasting glucose test results. In this group of patients death risk was increased (relative risk 1.8 in men and 2.6 in women). The death risk was significantly higher in patients with impaired glucose tolerance (glycemia 140–200 mg% in OGTT) and a normal fasting glucose test. Therefore the fasting glucose test does not allow the straightforward identification of the group of patients in high risk of premature death. The FPG does not show an independent association with mortality, however the 2-hour postprandial blood glucose test is an independent mortality predictor after fasting glucose correction [23].

Thus it should be emphasized that the presented analysis was not dedicated to the verification of current diagnostic criteria, but to defining the high risk group of patients with diabetes type 2. The probability of normal FPG was higher in the young and obese diabetic patients, whereas the older and slim patients more likely meet the 2-hour postprandial blood glucose criterion.

The DECODE observation initialized a new direction in research on influence of hyperglycemia on atherosclerosis oc-

currence and progression, indicating the significance of postprandial glucose. The conclusions, for the European population, were confirmed in other epidemiological studies [24,25].

The independent connection between postprandial glucose and newly diagnosed diabetic patients mortality was observed in an 11-year prospective observation - the Diabetes Intervention Study. The study shows that incidence of myocardial infarction in patients with postprandial glucose above 180 mg% (10 mmol/l) was 40% higher than in patients with postprandial glucose below 144 mg% (8 mmol/l). The key role in the evaluation of new diagnostic criteria value has the cause-effect link between hyperglycemia and cardiovascular diseases [26].

The Hoorn study showed the increasing cardiovascular risk in FPG equal to or above 110 mg% (6.1 mmol/l). Moreover, in non-diabetic patients without any cardiovascular diseases, the two standard deviations increase in the WHO glucose test predicted 2.24-fold increase of the total mortality relative risk and 3.4-fold increase of the cardiovascular mortality risk comparing with the general population [27]. The correlation remained statistically significant after including known cardiovascular risk factors.

Similarly, the Honolulu Heart Study and the Rancho Bernardo Study indicate a continuously increasing risk of coronary heart disease, while increased postprandial glucose levels were observed [28,29]. Another study, the Funagata Study, after 7 years of prospective observation, proved the impaired glucose tolerance instead of the abnormal FPG to be a cardiovascular risk factor [30].

In summary, more and more data suggest that both fasting and postprandial hyperglycemia are vascular pathology risk factors with the continuous risk increase. The 2-hour postprandial blood glucose identifies patients with the increased cardiovascular risk, not identified with the FPG test.

The review of studies concerning the causality between postprandial glycemia and cardiovascular disease is shown in table 1 [31].

The significance of postprandial hyperglycemia has to be confirmed in interventional studies to prove whether the postprandial glycemia normalization strategy is superior to the previous one focused on fasting and preload glycemia normalization. In chronic diseases unequivocal results may be obtained in long-term controlled clinical studies. By the time of an unequivocal confirmation in the interventional studies, the postprandial glucose normalization strategy in everyday clinical practice seems to be reasonable.

The de Vecciana et al. study [32] is the so far only study showing normalization of postprandial glycemia to be a predictor of diabetes compensation and reduction of diabetes-related pregnancy and perinatal complications. The study included 66 pregnant women with diabetes, requiring insulinotherapy before 30 weeks of pregnancy. The participating women were divided in two groups: in the first group the preload glucose was monitored and in the second group the FPG – 1 hour after each meal. In the group with postprandial glucose monitoring better metabolic compensation, less caesarian sections because of feto-pelvic disproportion and higher insulin requirement were observed. However, in the newborns of postprandial monitored mothers, the lower birth weight and less frequent hypoglycemia were observed. The beneficial effect was obtained by modification of the glucose level monitoring leading to insulinotherapy intensification in well-educated patients (significant higher insulin dose). In the study the two monitoring plans, not the therapeutic interventions were compared. However, it may be assumed that postprandial monitoring convinced the patients to adequately higher insulin injections.

The data obtained may not be extrapolated to late diabetes complications which occur after longer than the mentioned time of observation and require a long-term clinical study. On the other hand, in the presented study, a significant clinical improvement was obtained in a small group of patients and in a relatively short follow-up.

Practical aspects

Intensive treatment of diabetes with maintaining appropriate low glucose levels allows decreasing micro- and macroangiopathic complication risk. The best outcome is to achieve glucose levels in a normal range. Currently, glycosylated hemoglobin (HbA_{1c}) constitutes the main parameter to determine diabetes compensation. The Diabetes Association treatment guidelines include HbA_{1c} as recommended target values. In the European Association for the Study of Diabetes (EASD) and the ADA 2006 joint guidelines the recommended HbA_{1c} level is below 7% [33]. The Polish Diabetes Association recommends lower values ≤6.55 or even ≤6.1% [34]. The HbA_{1c} value reflects the mean glucose level during the last 8 weeks. The HbA_{1c} is influenced by the nocturnal blood glucose, preload and postprandial glucose level. In everyday clinical practice the FPG and preload glucose tests are recommended while the postprandial glucose is neglected. This pattern of diabetes control is obligatory in many diabetes outpatient clinics and hospital wards and any treatment correction must be based only on that parameters.

The mutual dependence between the HbA_{1c} value and postload glucose was described in 1978, by the time the HbA_{1c} became a routine evaluation in diabetic patients. Santiago et al. showed then the unequivocal positive correlation between HbA_{1c} and the 1- and 2-hour oral glucose tolerance test. The analyzed population included patients with normal blood glucose, impaired glucose tolerance and those meeting diabetes diagnostic criteria [35]. In 1999 the correlation between HbA_{1c} and 2-hour glucose results from the oral glucose tolerance test proved to be more pronounced than for FPG in a group of patients with type 2 diabetes [36]. Bonara et al. in the 2001 study showed the pronounced positive correlation between HbA_{1c} and the mean diurnal plasma glucose profile in the oral glucose tolerance test, and the mean preload and postload glucose result. The highest correlation was observed for the mean diurnal glucose value and a slightly higher for the preload than for the postload glucose. The correlation was much more legible in patients with home care than with clinic care mea-

Table 1. Cardiovascular complications associated with worsening of glycemia control [31]

Study	Parameter	Group		OR/HR/RR (95% CI)
Bedford Study	Fatal IHD	IGT comparing to control group	Male Female	OR 1.42 OR 5.16
Honolulu Heart Program	Fatal IHD	1-hour glucose level Quintile 5th comparing with quintile 1st		RR: 2.4* (1.3–4.6)
Islington Diabetes Study	IHD	2-hrs glucose		OR: 1.44 (1.06–2.00)
Chicago Heart Association Detection Project in Industry Study	Fatal CVD	1-hr glucose	White race Afro-Americans	RR: 1.18 (1.01–1.37) RR: 1.29 (0.61–2.72)
Whitehall, Paris Prospective & Helsinki Policemen Study	Fatal CVD	2-hrs glucose 97.5.–100. centile comparing with 0.–80. centile		RR: 1.3 (1.01–1.67)
Hoorn Study	Fatal CVD	2-hrs glucose 5.8 mmol/l (105 mg%) increase		RR: 3.0**
Funagata Diabetes Study	Fatal CVD	IGT *vs* NGT		HR: 2.22 (1.08–4.58)
DECODE metaanaliza	Fatal CVD	2-hrs glucose		HR: 1.27 (0.86–1.88)

* p <0,001, ** p <0,005

CVD – cardiovascular disease, IHD – ischemic heart disease, IGT – impaired glucose tolerance, NGT – normal glucose tolerance, OR – odds ratio, HR – hazard ratio, RR – relative risk

surements referring to all evaluated parameters. The probable reason is that the patients whose measurements were made in clinics might kept a diet more strictly on the days of visits to clinics than those who made their measurements at home [37]. Moreover, in patients with type 1 diabetes, HbA_{1c} and glucose blood levels from the different times of a day showed a clear correlation [38]. The patients treated according to the intensive insulinotherapy schedule, performed the 6-point glucose profile evaluating fasting, after breakfast, before and after lunch, before and after supper blood glucose levels. All the measurements defining the mean diurnal glucose blood level, the mean glucose preload level and the mean glucose postload level showed a strong positive correlation with the HbA_{1c} level, with the strongest correlation with the FPG, a glucose level test after breakfast and before supper.

An extraordinary interesting data were obtained from the continuous glucose monitoring system (CGMS) in children with diabetes type1. The three- consecutive- day survey showed that despite relatively good diabetes compensation (mean HbA_{1c} 7.7 ±1.4%) and preload glucose levels close to normal, the significant postprandial glucose level increase was observed. Nearly 90% of all postprandial measurements exceeded 180 mg/dl and 50% exceeded 300 mg/dl. The measurement with CGMS revealed asymptomatic prolonged nocturnal hypoglycemia with glucose levels >60 mg/dl in 70% of children [39].

The practical aspects of postprandial glucose level measurements were indicated in a large study of patients with type 2 diabetes who arrived to the outpatient clinic for the glucose blood level evaluation 1–4 hours after meal at home [40]. The mean HbA_{1c} level was 8.4 ±2.6%. In the majority of patients the diabetes compensation was insufficient because HbA_{1c} levels >6.5% in 77% of patients and ≥7.0% in 67% of patients were observed. In the study the correlation between HbA_{1c} and postprandial glucose was very significant ($r = 0.63$; $p < 0.001$). The correlation was stronger in patients with dietary and oral treatment; however, it was also seen in patients treated with insulin. HbA_{1c} levels correlating with the mean blood glucose level, in the 1–4 hour after a meal measurement are shown in table 2 [40]. In patients with glucose blood levels measured during the visit 150 mg/dl, surprisingly often HbA_{1c} level exceeded 8.0%. In patients with glucose >150 mg/dl after breakfast, the probability of HbA_{1c} level above 7.0% was high (>80%).

The study results show unequivocally that an inappropriate diabetes compensation may be predicted with a high probability in patients who have a slight postprandial hyperglycemia on the upper normal level regarded as acceptable. The blood glucose level exceeding 150 mg/dl measured in the outpatient clinic several hours after a meal seems to be the sign of inappropriate diabetes compensation and the indication to

treatment intensifying. That remains particularly important when the doctor does not know the current HbA_{1c} level or the patient does not submit to home glucose measurements. The therapeutic decision is usually unnecessarily delayed in such cases.

The higher is postprandial glucose contribution in hemoglobin HbA_{1c} the lower is HbA_{1c} concentration, therefore the better diabetes is compensated. That was showed in the Monnier et al. study where the patients with diabetes type 2 not treated with insulin were analyzed [1]. Fasting and between-meal blood glucose levels were evaluated. In the group with the highest HbA_{1c} (>10.2%) share of fasting glucose was 70%, whereas remaining glucose evaluation made 30%. In the groups with HbA_{1c} 7.3–10.2%, postprandial glucose contributed to 50–60% in the HbA_{1c} level. The highest contribution of postprandial glycemia came to 70% and was observed in the group with HbA_{1c} <7.3%. The dependence observed might have probably been even stronger and shifted toward postprandial glycemia if the blood glucose had been evaluated 1–2 hours after a meal, that is at the time of the maximal postprandial glucose concentration, not later [1].

The issue of postprandial glucose contribution to HbA_{1c} hemoglobin concentration have remained unnoticed for a long time. For years the importance of postprandial glycemia measurement has been underestimated by clinicians and the Diabetic Societies establishing diagnostic and treatment standards in diabetes. In 2001 the ADA guidelines remarked lack of clinical data for the standard postprandial glucose level evaluation in diabetic patients, with the exception of pregnant patients. In 2004 the ADA recommended the blood glucose level evaluation 1–2 hours after a meal in patients with normal preload glucose but HbA_{1c} above the upper normal limit with a purpose of obtaining glucose levels <180 mg/dl. The recommendations were repeated in consecutively published guidelines. According to the PTD guidelines published in 2005 and repeated in 2006–2007, glucose level monitoring should contain not only the HbA_{1c}, fasting and preload glucose evaluation but also the postload glucose measurement with the recommended postprandial glycemia level lower than 135 mg/dl.

Surprisingly, the postprandial glycemia evaluation has existed in standard procedure since recently. Even more surprises the lack of postprandial glucose evaluation in a routine care in many centers. Without these data the correct oral drugs or insulin dose matching seems to be impossible. Unsolved remains the issue of frequency of the postprandial glucose tests since there are no recommendations in the published standards. In 2007 the PTD introduced the guideline of glucose profile with the 2-hour after a meal glucose test to be performed at least once a week in patients treated with insulin and once a month in patients treated with oral medications [34].

The epidemiological data indicate that the assumed goals in diabetes treatment are achieved in the minority of patients. In the USA 37% of diabetic adult patients have HbA_{1c} exceeding 8% and 14% of patients – even 10% [41]. In Sweden, with the best metabolic diabetes compensation results, HbA_{1c} >7.5% are observed in 27% of patients with type 2 diabetes [43]. The routine of postprandial glycemia monitoring seems to allow glucose and HbA_{1c} normalization achievement. However, the monitoring must coexist with a change of diet and a possible treatment change or intensification. The postprandial glycemia drug target is acarbose, short-acting amplifier of insulin secretion such as repaglinid and nateglinid and fast-acting insulin analogs.

In summary, there are substantial evidences that postprandial hyperglycemia is significant in diabetes complication development, especially macroangiopathy. High glucose postprandial levels may reflect in HbA_{1c} concentration. Relatively low HbA_{1c} levels do not necessarily mean that the postprandial glucose check-up is sufficient. There is a need for fasting and postprandial glucose blood level monitoring and therapy modification with the purpose of achieving the recommended HbA_{1c} concentration and stable normalization of glucose diurnal level.

Table 2. Reciprocal relationship between hemoglobin HbA_{1c} concentration and the mean glucose blood level in type 2 diabetes 1–4 hours after a meal [40]

Mean glucose blood level 1–4 hours after meal	HbA_{1c}
105 mg/dl	7.0%
153 mg/dl	8.0%
201 mg/dl	8.8%

HbA_{1c} – glycosylated hemoglobin

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