

Editorial

New insights on glucose homeostasis during Ramadan

Keywords: Glucose homeostasis; Ramadan; Dietary intake

In this issue of *Diabetes & Metabolism*, Lessan et al. [1] report their experience in patients with diabetes (mostly type 2) who were investigated and compared during Ramadan and non-Ramadan periods. There is cogent evidence that Ramadan fasting disturbs the routine dietary habits of people with diabetes. As mentioned by Lessan et al. [1], the Ramadan fast entails a major shift in the timing and content of meals. It is currently admitted that, in normal conditions such as the absence of any intercurrent disease or illness, the nutrient intakes of people with diabetes should be closely similar to those recommended for the general population of healthy, non-diabetic individuals [2,3]. Weight-maintaining diets are usually prescribed for those who have body weights within the normal range, while calorie-restricted diets are generally implemented in those who are overweight or obese [2,3]. In addition, dietary carbohydrates should be distributed throughout the day by spreading nutrient intakes over regular time intervals for the three main meals and, eventually, by additional snacking at mid-morning and/or mid-afternoon times and at bedtime as appropriate.

In addition, by combining these dietary recommendations with better due consideration of the glycaemic index of foods [4], it has been demonstrated that it is possible to decrease HbA_{1c} levels at least by 1% (one percentage point), even in those with type 1 diabetes being intensively treated with either insulin pumps or basal–bolus insulin regimens [5]. However, as mentioned above, all recommendations related to the quantity and quality of carbohydrates (the glycaemic load) are usually far from fulfilled during the Ramadan period, which is characterized by both abstinence from eating and drinking from dawn to sunset, and no food or fluid restriction between sunset and dawn [6].

The transition from the fasting to the refeeding period is marked by the consumption of a sunset meal that breaks the fasting state. In the United Arab Emirates, the content of this sunset (*iftar*) meal has been estimated to provide an average intake of energy and carbohydrates of 1400 kcal and 160 g, respectively [1]. Therefore, using continuous glucose monitoring, it

is not surprising that a sudden and steep rise in glucose levels was observed by Lessan et al. [1] in all subsets of patients, irrespective of the type of antidiabetic therapies used.

1. Metabolic homeostasis during Ramadan and consequences for drug treatments

After a 12- to 15-h fast, the usual duration of abstinence from eating and drinking during Ramadan, both non-diabetic and diabetic people enter the “real” fasting state after a stepwise transition throughout several metabolic stages [7–9]. The nocturnal eating period is followed by a postprandial state that begins with the last food intake, usually at dawn. During this nocturnal period, any dietary carbohydrates ingested are progressively hydrolysed in the intestines, absorbed as monosaccharides and poured into the systemic circulation for further metabolism in extrahepatic tissues or stored in the liver as glycogen. Each 4-h postprandial period is followed by a 6-h postabsorptive state, which is metabolically characterized by progressive breakdown (glycogenolysis) of the glycogen stored in the liver during the preceding postprandial period [8,9].

Consequently, all those who have taken their last meal at dawn and not eaten during the daylight hours are in a genuine fasting state at the time of the sunset meal. This latter state is characterized by a progressive shift from glycogenolysis to gluconeogenesis (glucose derived from lactate, alanine and glycerol) and by an increased release of free fatty acids from adipose tissue and, subsequently, an increased production of ketone bodies (Fig. 1) [7]. In insulin-using diabetic patients, especially those with type 1 diabetes, such metabolic changes increase the risk of developing ketoacidosis. This complication does not arise in patients with type 2 diabetes treated with oral antidiabetic drugs (OADs), but it cannot be totally excluded in insulin-requiring patients with type 2 diabetes. Usually, in such patients, abstinence from eating during the daylight hours puts them at risk of either hypoglycaemic episodes or exaggerated hyperglycaemia, depending on whether the dosages of

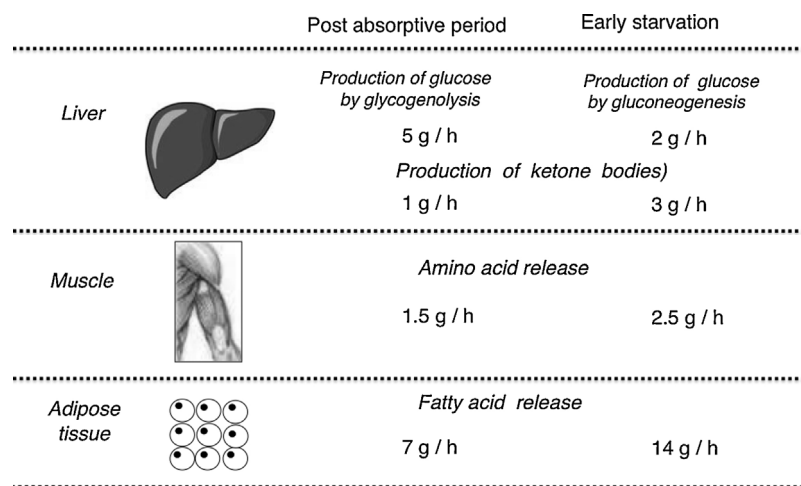


Fig. 1. Utilization and production of metabolic fuel in normal, healthy people during the postabsorptive state and early starvation [7].

antidiabetic medications (sulphonylureas or insulin) have been insufficiently or excessively reduced [6]. For this reason, sulphonylureas are usually considered unsuitable during Ramadan.

As a consequence, short-acting insulin secretagogues (glinides) or glucose-dependent insulinotropic agents [dipeptidyl peptidase (DPP)-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists] should serve as substitutes for ongoing therapy with long-acting non-glucose-dependent insulin secretagogues such as sulphonylureas [6,10]. In patients treated with insulin, however, it is usually recommended to reduce overall daily dosages and, more specifically, the doses injected at the dawn meal (*suhoor*) [11]. Furthermore, it is worth noting that the majority of the overall dose should be delivered before the sunset (*iftar*) meal [11] in patients treated with either twice-daily biphasic insulin regimens or multiple daily insulin injections.

In the study by Lessan et al. [1], the overall daily dose of insulin was reduced by 8% during Ramadan. Given the fact that this apparently small reduction was able to maintain satisfactory glycaemic control, it raises the question of whether the usual advice to reduce insulin doses by 20–30%, as reported by Lessan et al. [1] and others [11], is not somewhat exaggerated.

2. A typical case report and its integration into general considerations for Ramadan

In September 2008, we, at the outpatients’ clinics of the University Hospital (Montpellier, France), had the opportunity to investigate a subject on an ambulatory basis, using continuous glucose monitoring technology, during Ramadan. The subject’s daily glucose pattern (Fig. 2) was similar to those observed by Lessan et al. [1], including a dietary intake of carbohydrates at the sunset meal that was followed by a rapid and exaggerated increment in glucose levels. Within a time interval of < 2 h, glucose concentrations rose from 130 mg/dL to ≥ 400 mg/dL, and plateaued at an average level of 400 mg/dL overnight until dawn. During the Ramadan period, this patient, who was usually treated (in non-Ramadan periods) with a twice-daily insulin glargine regimen (58 and 20 units before breakfast and dinner, respectively) was instructed to take a single daily dose of insulin

just before the sunset meal, which combined 44 units of insulin glargine and 16 units of short-acting insulin glulisine. Yet, the potency of this high predinner dose of insulin to control blood glucose excursions after the sunset meal was largely annihilated and overcome by a carbohydrate intake that was probably too high a level for the sunset meal, and this high level was further maintained throughout the nocturnal period. At dawn and throughout the subsequent daylight hours, this patient continued to exhibit high circulating concentrations of glucose as a result of the continuous and sustained nocturnal overfeeding.

To deal with this situation, the patient took a single dose of insulin (44 units of glargine and 16 units of glulisine) injected at the sunset meal several hours before the beginning of the diurnal period. As illustrated in Fig. 2, the rate of glucose disappearance was relatively constant throughout the period from 08h00 to 20h00, with a progressive glucose decrement from 400 to 130 mg/dL. The long delay required to obtain a near-normal glucose concentration in the late afternoon indicated that a single injection combining prandial and basal insulin analogues at the evening meal on the preceding day was not sufficient to achieve satisfactory 24-h glycaemic control in the face of frank nighttime overeating. Given the latter situation, it might be better to recommend a basal–bolus regimen with injection of an appropriate dose of a rapid insulin analogue before the dawn meal. Another alternative would be to use a twice-daily regimen combining the injection of basal and prandial insulin preparations at both the sunset and early-morning meals, especially when the latter also provides a significant intake of carbohydrates.

In fact, according to our observations, it is highly likely that the carbohydrate loads at both the sunset and dawn meals largely exceeded the total body glucose-uptake capabilities (2 mg/kg/min) usually observed during the postabsorptive state in normal healthy people [12]. Bringing together our case report and the observations of Lessan et al. [1], it appears that both the exaggerated glucose excursions after the sunset meal and the sustained overnight hyperglycaemia are the two main glycaemic disorders encountered during Ramadan. However, the findings of Lessan et al. [1] appear to be somewhat reassuring as those investigators found that the impact of such glycaemic

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