Type 2 Diabetic Patients Fasting on Ramadan in Israel

Zaina Adnan MD

Institute of Endocrinology and Metabolism, Zvulon Medical Center at Clalit Medical Services, Kiryat Bialik, Israel

ABSTRACT: Fasting during Ramadan is not mandatory for diabetic patients, but the majority of type 2 diabetic patients insist on fasting despite the potential risks. These patients represent a challenge not only for themselves, but also for health care practitioners during this period. This review provides, for the first time, health care practitioners in Israel with guidelines and recommendations that fit the Muslim population for better management of diabetic patients who fast during Ramadan, taking into consideration recently published recommendations and therapies available in Israel.

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KEY WORDS: type 2 diabetes, risk category patients, Ramadan, incretin-based therapy, insulin therapy

Ramadan is the ninth month of the Islamic calendar, and fasting during this time represents one of the five pillars in Islam. Fasting during the holy month of Ramadan is obligatory for all healthy adult Muslims and requires abstinence from eating, drinking and smoking each day from sunrise to sunset. During Ramadan Muslims consume two main meals: a pre-dawn meal (*Suhoor*) and a fast breaking meal after sunset (*Iftar*).

The prevalence of diabetes in the general population is increasing rapidly, with 415 million patients diagnosed by 2015. This number is expected to rise to 642 million by the year 2040. The number of people with type 2 diabetes is increasing globally and the majority of these people live in low- and middle-income countries [1]. In Israel, Muslims comprise about 18% of the general population and account for approximately 1.5 million individuals. According to the Israeli National Health Interview Survey (INHIS-3 2013–2015) the estimated prevalence of diabetes in the Arab population is higher than the overall prevalence of diabetes in Israel (10.3% vs. 8.4%). Data from epidemiological studies found that about 78.7% of type 2 diabetic patients fast during Ramadan. Therefore, it can be estimated that at least 100,000 patients with type 2 diabetes in Israel fast during Ramadan [2].

MAJOR RISKS ASSOCIATED WITH FASTING DURING RAMADAN

HYPOGLYCEMIA

Hypoglycemia represents one of the major acute complications associated with fasting during Ramadan. Abstaining from food intake, unadjusted anti-diabetic agents and lack of pre-Ramadan instructions are factors which might lead to hypoglycemic events.

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed that fasting during Ramadan increases the risk of severe hypoglycemia requiring hospitalization by 4.7-fold, increasing in patients with type 1 diabetes from 3 to 14 events per 100 people; and sevenfold in patients with type 2 diabetes, from 0.4 to 3 events per 100 patients during the month of Ramadan [3].

The incidence of severe hypoglycemia may have been underestimated because events requiring assistance from a third person without the need for hospitalization were not included. However, this study [3] was conducted before the introduction of new classes of agents with less hypoglycemic events, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor (GLP-1Rc) agonists. Most patients experiencing a hypoglycemic event were treated with oral hypoglycemic agents and insulin.

A recently published multi-country retrospective observational study of the management and outcome of patients with diabetes during Ramadan reported a low incidence of hypoglycemic events: 8.8% of type 2 diabetic patients reported at least one episode and a symptomatic hypoglycemia rate of 6.36% [4].

HYPERGLYCEMIA

Hyperglycemia during Ramadan fasting represents another important concern due to changes in habitual eating: a large amount of food is ingested at Iftar causing postprandial hyperglycemia in addition to the reduction of anti-diabetic oral agents and unadjusted insulin treatment without guidance from a medical professional. It is well known that postprandial hyperglycemia is an independent cardiovascular risk factor and is linked to endothelial dysfunction and increased oxidative stress [5]. Thus, it is important to prevent hyperglycemia during fasting, and especially after Iftar.

WEIGHT GAIN

Weight gain during Ramadan may occur due to multiple factors, such as increased carbohydrate intake at the Iftar and Suhoor meals, decreased physical activity, increased insulin dosing without self-glucose monitoring, as well as lack of medical instructions and Ramadan-focused education for healthcare practitioners during the pre-Ramadan period. Recently published data of the Ramadan Education and Awareness in Diabetes (READ) program disclosed a 0.7 kg ($P < 0.001$) weight reduction in the

education group during Ramadan, while patients in the control group gained about 0.6 kg. The introduction of a "conversation map" tool, specifically designed to assist diabetic patients who fast during Ramadan, as well as the use of agents with neutral or lower weight effects, such as DPP-4 inhibitors and GLP-1Rc agonists largely administrated in Israel, are beneficial in controlling weight gain [6].

DEHYDRATION AND THROMBOSIS

Prolonged fasting and limitation of fluid intake may predispose diabetic patients to dehydration and volume depletion. Factors that may exacerbate this condition include excessive perspiration in a hot climate, strenuous physical activity, increased osmotic diuresis due to uncontrolled hyperglycemia, and vomiting associated with headache and migraine [7]. Patients may suffer from orthostatic hypotension associated with falls and fractures, and thus, attention should be given to elderly patients known to have osteoporosis.

In addition, volume depletion and intravascular contraction may predispose patients to a hypercoagulability state, with increased incidence of thrombosis. Increased incidence of retinal vein thrombosis was previously reported by Alghadyan [8].

Patients with diabetes, even without macrovascular complications, are prone to a hypercoagulability state. High levels of coagulation factors II, V, VII, and X with low levels of anti coagulant protein C were major contributing factors that enhanced thrombin generation. Of interest, a high blood glucose level was correlated with shortened clotting time, reflecting the association between hyperglycemia and hypercoagulability [9].

RISK STRATIFICATION OF PATIENTS WITH DIABETES BEFORE RAMADAN FASTING

Risk stratification categories are important for healthcare practitioners to evaluate patients who plan on fasting. New guidelines have been published based on previous classification categories of risk in patients with type 1 and type 2 diabetes who fast during Ramadan, including the published consensus statements in 2005 by the American Diabetes Association (ADA) updated in 2010 [12,13] and recent practical guidelines published by the International Diabetes Federation and Diabetes Ramadan International Alliance (IDF-DRA) in April 2016 [14]. These guidelines considered parameters such as fasting plasma glucose level, hemoglobin A1C, renal function including estimated glomerular filtration rate (eGFR), and urinary albumin excretion in addition to anti-diabetic therapy, duration of diabetes and hypercoagulability states. The present classifications focus on the parameters in each risk category, providing healthcare practitioners with more precise information about patient status. These classifications are based on the high incidence of hypoglycemia in patients with a long duration of diabetes and for whom therapies have become more complex. Physiological and behavioral defenses against hypoglycemia become attenuated, as well as an increase in cardiovascular events in correlation with kidney function decline and increased excretion of urinary albumin [15]. Therefore, patients with nephrotic syndrome, independent of their eGFR, are categorized as very high risk due to an increased risk of thrombosis secondary to multiple factors [16]. Patients living in hot climates, like the Bedouin in the Negev Desert area of southern Israel, have been classified in the high-risk category for fasting during Ramadan. Table 1 summarizes categories of risk in diabetic patients who fast during Ramadan.

MANAGEMENT OF DIABETIC PATIENTS DURING RAMADAN

The current study focuses on anti-diabetic agents and therapies available in Israel. Treatment for diabetic patients who fast during Ramadan should be individualized. Generally, agents with lower hypoglycemic events and weight-lowering or neutral effects are recommended.

Pre-Ramadan medical assessment

The pre-Ramadan period begins 1–2 months before the month of Ramadan. During this period HPC should prepare diabetic patients who want to fast during Ramadan so that they can withstand the Ramadan period safely. Three important elements should be included during this period:

- General campaign including meetings and media advertising campaigns for diabetic patients, healthcare practitioners, and religious and community leaders to increase their awareness of healthy fasting practices
- Ramadan-focused educational programs for patients with diabetes
- Ramadan-focused educational programs for healthcare practitioners

Healthcare practitioners should be trained to deliver structured patient educational programs that include understanding of fasting and diabetes in general as well as adjustments for individualized therapy. These programs should include an explanation about the importance of glucose monitoring during fasting and non-fasting hours, whether to stop fasting, meal planning and content to avoid hypoglycemia and dehydration during prolonged fasting, and meal types to avoid postprandial hyperglycemia and weight gain.

Ramadan-focused educational programs should include advice on the timing and intensity of physical activity, for example avoiding physical activity or intensive physical work especially during the last few hours of fasting. One of the advances in this field is the introduction of a "conversation map" tool for diabetic patients who are fasting during Ramadan. This tool was

Table 1. Risk categories of patients with diabetes who fast during Ramadan

Very high risk
- Type 1 diabetes
- Pregnancy
- Diabetic ketoacidosis within 3 months of Ramadan
- Hyperosmolar hyperglycemic coma within 3 months of Ramadan
- Severe recurrent hypoglycemia within 3 months of Ramadan
- Hypoglycemia unawareness
- Sustained poor glycemic control
- Average blood glucose ≥ 300 mg/dl or HbA1C ≥ 10%
- Acute illness one month prior to Ramadan which necessitated hospitalization
- Intense physical labor while on insulin and sulfonyluria
- Chronic kidney failure stage 4 and 5 with or without albumin excretion*
- Diabetic patients with nephrotic syndrome† independent of eGFR and HbA1C
- Disease duration more than 20 years

High risk
- Moderate hyperglycemia
- Average blood glucose 300–250 mg/dl or HbA1C 10–9 %
- Chronic kidney failure stage 3 with moderate GFR decline of 30–59 ml/min/1.73 m^2 with micro- or macroalbuminuria
- Advanced macovascular complications
- Living alone and treated with insulin or sulfonylurea
- Patients with co-morbid conditions that present additional risk factors
- Very old age with ill health
- Treatment with drugs that may affect awareness
- Bedouins living in remote areas with limited water supply and minimal access for healthcare
- Patients on insulin treatment as basal bolus or mixture insulin › 2 injections/day
- Disease duration of 20–15 years

Moderate risk
- Mild hyperglycemia
- Average blood glucose 200 mg/dl or 7.5% ‹ HbA1C ≤ 9%
- Diabetic patients with short-acting insulin secretagogues and sodium glucose co-transporter inhibitors
- Patients moderately controlled on basal or basal plus or mixture insulin ≤ 2 injections daily
- Chronic kidney disease stage 2 with mild GFR decline of 60–89 ml/min/1.73 m^2 with or without microalbuminuria
- Disease duration 15–10 years

Low risk
- Average blood glucose 150 mg/dl or HbA1C ≤ 7.5%
- Patients treated with diet and modified lifestyle
- Anti diabetic agents including: metformin, acarbose, TZDs, incretin based therapy with normal GFR and normoalbuminuria
- Disease duration less than10 years

*Albumin excretion defined as normal albumin excretion ‹ 150 mg/d, ‹ 30 µg/mg albumin-to-creatinine ratio. Microalbuminuria 150–300 mg/d, or 30–300 µg/mg albumin-to-creatinine ratio. Macroalbuminuria › 300 mg/d; › 300 µg/mg albumin-to-creatinine ratio.

†Nephritic syndrome defined as urinary protein excretion › 3.5 g/d, hypoalbuminemia ‹ 3.0 g/d and edema

HbA1C = hemoglobin A1C, eGFR = estimated glomerular filtration rate, TZDs= thiazolidindiones, GFR = glomerular filtration rate.

This classification is based on expert opinion and previous classifications published recently

published in 2013 and supported by Eli Lilly and Company, a global pharmaceutical company based in the United States, in collaboration with the International Diabetes Federation. This tool has been implemented for patients in more than 40 countries including Israel [6].

DIET CONTROL

The risk of fasting during Ramadan for patients who control their diabetes with diet is very low. Because postprandial hyperglycemia may occur after the pre-dawn and sunset meals, measuring blood glucose 2 hours after these meals is highly recommended. Moreover, physical activity should be practiced only after the sunset meal to prevent postprandial hyperglycemia.

METFORMIN

Metformin is the most commonly used first-line agent to treat type 2 diabetic patients. The risk of hypoglycemia is very low for patients who have been prescribed monotherapy. At present two formulations are in use: metformin immediate release (IM) preparation as a single compound and metformin extended release (XR) in compound, and several DPP-4 inhibitors. For patients treated with the maximum dose of metformin IR (850 mg per tablet), dosages of one tablet at Suhoor and two tables after Iftar are recommended.

SULFONYLUREAS

Sulfonylureas stimulate insulin secretion from beta cells in a glucose-independent manner. Patients treated with this group of agents are prone to hypoglycemia, which can sometimes be severe. Despite the high rate of hypoglycemia, sulfonylureas are still in use because of their low cost. Reported data disclosed different results regarding hypoglycemia among this group of agents. Second-generation sulfonylureas like glimepride or glipizide are preferred over conventional sulfonylureas such as glibenclamide. During Ramadan caution is needed when recommending sulfonylureas. Physicians might consider changing medications to agents with a low risk of hypoglycemia during the pre-Ramadan period [17].

SHORT-ACTING INSULIN SECRETAGOGUES

Insulin secretagogues such as repaglinide stimulate insulin secretion from pancreatic beta cells. These agents are suitable and safe for use during the month of Ramadan because of their short active duration. Small observational studies have shown no hypoglycemic events with this treatment during Ramadan. Treatment with these agents seems to be more favorable than conventional sulfonylureas during Ramadan [18].

THIAZOLIDINDIONES

Thiazolidindiones (TZDs) increase glucose uptake in different tissues, particularly adipose tissue, by activating peroxisome proliferator-activated receptor gamma. Pioglitazone is not associated with hypoglycemia when administered with metformin. However, hypoglycemia occurs when these agents are administered with other agents that induce hypoglycemia, such as sulfonylureas and insulin. Weight gain and increased risk of bone fractures should be considered when prescribing these agents, especially in elderly patients. It is contraindicated in patients

with advanced congestive heart failure. In general, these agents are suitable for use during Ramadan. However, limited clinical data are available on their use during Ramadan [19].

ALPHA-GLUCOSIDASE INHIBITORS

Alpha-glucosidase inhibitors such as acarbose slow the absorption of carbohydrates when taken with meals by inhibiting the action of alpha-glucosidase enzymes in the intestinal brush border. These agents are useful during Ramadan. However, they exert a modest effect on postprandial glucose and a minimal effect on fasting glucose. Therefore, combination therapy with other agents that decrease fasting plasma glucose is recommended. Due to gastrointestinal side effects such as flatulence, it is recommended to initiate the therapy with low doses. No dose adjustment for acarbose is needed during Ramadan fasting.

INCRETIN-BASED THERAPY

DPP-4 inhibitors increase circulating levels of endogenous GLP-1 hormones by blocking the action of these enzymes, which in turn increase insulin and decrease glucagon secretions in a glucose-dependent manner. Therefore, hypoglycemia is rare with this group of agents. DPP-4 inhibitors such as sitagiptin, vildagliptin, saxagliptin and linagliptin are available in Israel. Due to the low rate of hypoglycemic events and the neutral weight effect, this group of agents is preferred for use during Ramadan.

Sitagliptin and vildagliptin were the only DPP-4 inhibitors widely studied during Ramadan [20,21]. DPP-4 inhibitors, in combination with metformin extended release or with metformin immediate release, represent some of the most favorable therapies during Ramadan. It is recommended that this therapeutic regimen be administered with, or immediately after, the Iftar meal.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

The mechanism of action of GLP-1Rc agonists increases insulin and decreases glucagon secretions in a glucose-dependent manner. In addition, these agents decrease body weight by suppressing appetite and slowing gastric emptying. In this group, five agents are already in use in Israel; two agents (exenetide and lixisenatide) are considered short-acting GLP-1Rc agonists. The other three (liraglutide, exenatide LAR and dulaglutide) are considered long-acting GLP-1Rc agonists. GLP-1Rc agonists should be initiated during the pre-Ramadan period, taking into account the drug titration period, time to achieve a therapeutic steady-state concentration of the drug, and adverse side effects. Therefore, it is recommended that therapy be initiated at least 1 month before the start of Ramadan fasting to prevent gastrointestinal side effects and to achieve a therapeutic steady-state concentration. This new class of agents is favorable for use during Ramadan, especially due to the low rate of hypoglycemia and the weight reduction effect. Among long-acting GLP-1Rc agonists, liraglutide is the only agent to have been studied during Ramadan [22].

SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS

Sodium glucose co-transporter 2 (SGLT2) inhibitors increase glucose excretion through selective inhibition of SGLT2 on the first segment of the proximal tubule of the nephron. Dapagliflozin and empagliflozin are available in Israel. To the best of my knowledge, only one study with dapagliflozin has been published regarding effectiveness during Ramadan [23]. Thus cautious use is recommended during Ramadan, especially in elderly patients.

INSULIN TREATMENT

Many patients who fast during Ramadan are treated with one long-acting insulin injection. It is well known that the use of long-acting insulin analogues such as detemir and glargin U100 with fewer hypoglycemic events are more favorable than human intermediate-acting insulin. Recently, insulin degludec and insulin glargin U300, with their ultra-long action, were included in the healthcare basket of treatments in Israel and are available for use. These two agents, with their prolonged half-life action, lower glucose variability and hypoglycemia, especially at night, and therefore seem to be more favorable for use during Ramadan. Postprandial hyperglycemia after the sunset meal is frequent during Ramadan due to high caloric intake at this meal. Therefore, short-acting insulin might be considered during or immediately after Iftar [24].

Many Muslims with diabetes are passionate about fasting during Ramadan. This passion represents an opportunity to empower diabetic patients to better manage their glucose profile, including treatment intensification during the Ramadan period. In patients with well-controlled fasting plasma glucose, it is recommended to reduce the dose of long-acting insulin by 20%, while adding 6 to 8 units of short-acting insulin at the Iftar meal. Dose adjustment of the short-acting insulin should be based on the post-meal measured glucose. It is usually recommended to measure postprandial glucose after 2 hours. However, patients should be advised during Ramadan to adjust short-acting insulin dosage according to glucose level after the *Taraweeh* prayers, taking into account that these prayers resent mild to moderate physical activity. The use of insulin analog mixtures represents another modality of therapy in type 2 diabetic patients who prefer fewer injections and are less compliant with multiple daily insulin injections. According to Mattoo et al. [25], insulin analogue mixtures can be used during the Ramadan fasting. For better postprandial glucose control, it is recommended that the evening dose of an insulin mixture be changed to insulin that provides a higher percent of short-acting insulin, such as an insulin lispro mix 50 or insulin aspart mix 50, instead of an insulin lispro mix 25 or an insulin aspart mix 30 considering the high caloric and carbohydrate intake at the Iftar meal [Table 2].

Table 2. Summary of drug changes during Ramadan

Pre-Ramadan treatment	During Ramadan*
Diabetes well controlled with diet and lifestyle modification	Physical activity after fast-breaking meal (Iftar) or early in the morning
Metformin (biguanide) therapy	No change in therapy
DPP-4 inhibitors, alpha-glucosidase inhibitors (e.g., acarbose), thiazolidinediones (e.g., pioglitazone), SGLT2 (with and without metformin)	No change in therapy regimens For AGIs consider increase of evening dose according to post-meal glucose levels
Sulphonylureas with and without metformin: one dose per day in the morning twice per day (morning/evening)	Switch the same dose to evening before/during Iftar Reduce the predawn (Suhoor) dose to half and keep the same dose at Iftar Consider changing the dose according to daytime and post-meal glucose levels
Meglitinides: (repaglinide) with or without metformin	Reduce the predawn (Suhoor) dose to half and keep the same dose at Iftar Consider changing the dose according to daytime and post-meal glucose levels
GLP-1Rc agonists (with or without metformin or long-acting insulin)	No dose change Consider dose adjustment of long-acting insulin according to predawn (Suhoor) glucose levels
Insulin treatment: Basal regimen with one long-acting insulin injection (humulin N, insulotard, glargin U100, glargin U300, detemir, and degludec)	Consider adding a short-acting insulin analog (lispro, aspart, glulisine) of 6–10 units before Iftar (dose adjustment according to post-meal glucose level) Consider decreasing long-acting insulin by 20%
Basal plus regimen: one long-acting and one short-acting insulin dose before the main meal	Switch the short-acting insulin to the Iftar meal Consider dose adjustment (increase) according to post-meal glucose level and decreasing long-acting insulin by 10–20 percent according to fasting or Suhoor glucose level
Basal bolus regimen	Decrease the short-acting insulin during the predawn meal (Suhoor) by 30–50% and increase the insulin dose by 30–50% at Iftar (dose adjustment according to post-meal glucose)
Mixture insulin regimen: less recommended during Ramadan	Consider decreasing the dose of insulin at the predawn (Suhoor) meal by 30–50% and increasing the dose at the Iftar meal by 30–50% Consider switching to an insulin mixture at Iftar with one that provides high short-acting insulin (lispro mix 50 or insulin aspart mix) for controlling postprandial hyperglycemia

DPP-4 = dipeptidyl peptidase-4, AGIS = alpha-glucosidase, AGIs = alpha-glucosidase inhibitors, SGLT2 = sodium glucose co-transporter 2, GLP-1Rc = glucagon-like peptide-1 receptor

*These recommendations are based on clinical expert opinions and recently published recommendations.

ENDING RAMADAN FASTING

It is mandatory that anyone who suffers from any acute illness during Ramadan, including type 2 diabetes, end their fast. Diabetic patients with glucose levels lower than 70 mg/dl (3.8 mmol/L) and higher than 300 mg/dl (16.6 mmol/L) should stop their fast. Patients with self-monitoring blood glucose levels of approximately 80 mg/dl (4.4 mmol/mol) during the first hours of fasting should stop the fast, especially those using sulfonylureas and insulin therapy. In diabetic patients classified in the categories of moderate and low risk who are treated with metformin, incretin-based therapy, alpha-glucosidase inhibitors, and TZDs with documented results around 80 mg/dl (4.4 mmol/L) in the pre-Ramadan period and without symptoms of hypoglycemia might continue their fast. In this condition self-monitoring of blood glucose every few hours is obligatory and patients must break their fast if lower levels are observed.

CONCLUSIONS

Diabetic patients who fast during Ramadan, or other religious fasting days, should be evaluated by experienced healthcare practitioners with vast knowledge in this field. During the pre-Ramadan period, procedures for safer Ramadan fasting should be initiated. Patient risk stratifications should take into consideration other conditions not previously reported, such as duration of diabetes and the presence of nephrotic syndrome that might predispose patients to a hypercoagulability state. Fasting recommendations should be tailored to each individual and should consider population-specific conditions, such as nomadic Bedouin who live in isolated areas far from regular medical services. Socioeconomic status should also be recognized. Short-acting insulin secretagogues and second-generation sulfonylureas are preferred to conventional sulfonylureas. Ultra-long insulin agents with lower glucose variability and nocturnal hypoglycemia seem promising. Incretin-based therapy, including DPP-4 inhibitors and GLP-1Rc agonists in combination with metformin, represents the most favorable combination and modality of treatment.

Correspondence
Dr. Z. Adnan
Institute of Endocrinology, Zvulon Medical Center at Clalit Medical Services, Kiryat Bialik 2723901, Israel
Phone: (972-4) 878-7700
Fax: (972-4) 878-7568
email: zainaad@clalit.org.il

References

1. International Diabetes Federation. IDF Diabetes Atlas (Seventh Edition). 2015. http://www.diabetesatlas.org/resources/2015-atlas.html. Accessed April 1, 2017.
2. Israeli National Health Interview Survey. https://www.health.gov.il/UnitsOffice/ICDC/Health_Surveys/Pages/INHIS.aspx. Accessed April 1, 2017 (Hebrew).
3. Salti I, Bénard E, Detournay B, et al. A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan. *Diabetes Care* 2004; 27: 2306-11.
4. Babineaux SM, Toaima D, Boye KS, et al. Multi-country retrospective observational study of the management and outcomes of patients with type 2 diabetes during Ramadan in 2010 (CREED). *Diabet Med* 2015; 32: 819-28.
5. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008; 57: 1349-54.
6. Bravis V, Hui E, Salih S, et al. Ramadan Education and Awareness in Diabetes (READ) programme for Muslims with type 2 diabetes who fast during Ramadan. *Diabet Med* 2010; 27: 327-31.
7. Trabelsi K, Rebai H, El-Abed K, et al. Effect of Ramadan fasting on body water status markers after a rugby sevens match. *Asian J Sports Med* 2011; 2: 186-94.
8. Alghadyan AA. Retinal vein occlusion in Saudi Arabia: possible role of dehydration. *Ann Ophthalmol* 1993; 25: 394-8.

9. Kim HK, Kim JE, Park SH, et al. High coagulation factor levels and low protein C levels contribute to enhanced thrombin generation in patients with diabetes who do not have macrovascular complications. *J Diabetes Complications* 2014; 28: 365-9.
10. Ghafoor E, Riaz M, Eichorst B, et al. Evaluation of Diabetes Conversation Map™ education tools for diabetes self-management education. *Diabetes Spectr* 2015; 28 (4): 230-5.
11. Hassanein M, Bravis V, Hui E, Devendra D. Ramadan-focused education and awareness in type 2 diabetes. *Diabetologia* 2009; 52: 367-8.
12. Al-Arouj M, Bouguerra R, Buse J et al. Recommendations for management of diabetes during Ramadan. *Diabetes Care* 2005; 28: 2305–11.
13. Al-Arouj M, Assaad-Khalil S, Buse J, et al. Recommendations for management of diabetes during Ramadan: update 2010. *Diabetes Care* 2010; 33: 1895-902.
14. Diabetes and Ramadan: Practical Guidelines. http://www.daralliance.org/daralliance/wp-content/uploads/IDF-DAR-Practical-Guidelines_15-April-2016_low_1.pdf. Accessed April 2017.
15. Wang Y, Yuan A, Yu C. Correlation between microalbuminuria and ardiovascular events. *Int J Clin Exp Med* 2013; 25: 973-8.
16. Hull RP, Goldsmith DJ. Hull RP, Goldsmith DJ. Nephrotic syndrome in adults. *BMJ* 2008; 336 (7654): 1185-9.
17. Aravind S, Al Tayeb K, Ismail SB, et al. Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: a five-country observational study. *Curr Med Res Opin* 2011; 27: 1237-42.
18. Anwar A, Azmi K, Hamidon B, et al. An open label comparative study of glimepiride versus repaglinide in type 2 diabetes mellitus Muslim subjects during the month of Ramadan. *Med J Malaysia* 2006; 61: 28-35.
19. Vasan S, Thomas N, Bharani AM, et al. A double-blind, randomized, multicenter study evaluating the effects of pioglitazone in fasting Muslim subjects during Ramadan. *Int J Diabetes Dev Ctries* 2006; 26: 70-6.
20. Al Sifri S, Basiounny A, Echtay A, et al. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial. *Int J Clin Pract* 2011; 65: 1132-40.
21. Hassanein M, Abdallah K, Schweizer A. A double-blind, randomized trial, including frequent patient physician contacts and Ramadan-focused advice, assessing vildagliptin and gliclazide in patients with type 2 diabetes fasting during Ramadan: The STEADFAST study. *Vasc Health Risk Manag* 2014; 10: 319-25.
22. Azar ST, Echtay A, Wan Bebakar WM, et al. Efficacy and safety of liraglutide compared to sulphonylurea during Ramadan in patients with type 2 diabetes (LIRA-Ramadan): a randomized trial. *Diabetes Obes Metab* 2016; 18: 1025-33.
23. Wan Juani WS, Najma K, Subashini R, et al. Switching from sulphonylurea to an SGLT2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia. *Diabetes Obes Metab* 2016; 18 (6): 628-32.
24. Akram J, De Verga V. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 1999; 16: 867-74.
25. Mattoo V, Milicevic Z, Malone JK, et al. A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; 59: 137-43.

Capsule

What's in a drop of blood?

Blood contains many types of cells, including many immune system components. Immune cells used to be characterized by marker-based assays, but now classification relies on the genes that cells express. Villani and colleagues used deep sequencing at the single-cell level and unbiased clustering to define six dendritic cell and four monocyte populations. This refined analysis has identified, among others, a previously unknown dendritic cell population that potently activates T cells. Further cell culture revealed possible differentiation progenitors within the different cell populations.

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Eitan Israeli

Capsule

Oral microbiome may be linked to risk of certain cancers

Jiyoung Ahn, an associate professor of epidemiology at the New York University School of Medicine, presented research about links between the oral microbiome and the risk of certain cancers at the American Association for Cancer Research's annual meeting. In Ahn's research on pancreatic cancer, her team found that people who had higher levels of one type of oral bacteria, *Porphyromonas gingivalis*, had a 60% higher risk of developing pancreatic cancer than did people who had lower levels of these bacteria. Higher levels of another type of oral bacteria, *Aggregatibacter actinomycetemcomitans*, was linked to a more than doubled risk of pancreatic cancer, she said. There are also differences in the oral microbiomes of people with esophageal cancer compared with the oral microbiomes of people who do not have the disease. For example, people with esophageal cancer tend to have much lower levels of a type of bacteria called Proteobacteria. In both cases–pancreatic cancer and esophageal cancer–more research is needed to determine if there is a cause-and-effect relationship. Other factors, including smoking and alcohol, also may play a role. Both smoking and drinking alcohol can change the oral microbiome and indeed both are risk factors for esophageal cancer and pancreatic cancer.

Live Science 2017; http://www.livescience.com/58512-oral-microbiome-cancer-risk.html

Eitan Israeli

"In recognizing the humanity of our fellow beings, we pay ourselves the highest tribute"

Thurgood Marshall (1908-1993), American Supreme Court Justice and its first African-American judge