Caution is Needed in Interpreting Hemoglobin A1c Levels in the Muslim Bedouin Population of Southern Israel

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ABSTRACT: The Bedouins living in southern Israel are a Muslim-Arab population that is transitioning from a nomadic lifestyle to life in permanent settlements. The population has unique characteristics that could affect hemoglobin A1c (HbA1c) measurements. The objective of this study was to describe the socio-demographic and unique morbidity characteristics of this community and the effect on HbA1c measurements. Consanguinity, especially among cousins in the Bedouin population, results in a high prevalence of autosomal recessive genetic diseases such as thalassemia (underestimate of HbA1c), hemoglobinopathies (underestimate and overestimate), Gilbert’s disease, and glucose-6-phosphate dehydrogenase deficiency, an X-linked disorder, which can cause hyperbilirubinemia with an overestimate of HbA1c. Furthermore, nutritional deficiencies, autosomal recessive diseases, high birth rates, parasitic infections, and poverty can all cause high rates of anemia (iron and vitamin B12 deficiencies) that can raise HbA1c levels. Congenital dyserythropoietic anemia is found among Bedouin tribes in the Negev region and can lead to an underestimation of HbA1c levels. Pregnancy can also affect HbA1c levels. Medical teams working in the Bedouin community and in other Muslim populations with similar morbidity characteristics throughout the world should identify patients with medical conditions that can affect HbA1c measurements and be aware of possible measurement alternatives such as fructosamine and glycated albumin.

KEY WORDS: Bedouin, diabetes mellitus, hemoglobin A1c (HbA1c), Muslim

I sraeli Bedouins, who represent 3.5% of the overall population of Israel, are one of the ethnic Arab groups in Israeli society. Most of the Bedouins reside in the Negev region of southern Israel. Some of the 220,000 Negev Bedouin live in permanent cities and towns, some in unrecognized villages and others as semi-nomads. The Bedouins have unique ethnic customs. Phenomena such as polygamy and high birth rates (the mean number of children is 6.8) are very common. These characteristics interlace with the modern Israeli lifestyle, leading to a “population in transition” [1]. The Bedouin population has the lowest socio-economic level in Israel [1]. The rates and characteristics of acute and chronic diseases in this population are unique. The rate of diabetes mellitus is much higher than in the Jewish population (12% vs. 8%, respectively) and adherence rates to treatment are lower (42% vs. 27%, respectively) [2]. Among the health gaps that exist between various populations in Israel, the control of diabetes mellitus presents a difficult challenge to government plans to reduce these gaps [3]. The measurement of hemoglobin A1c (HbA1c) levels has become the gold standard for monitoring and controlling diabetes mellitus. Its use has been extended in recent years for the diagnosis and screening for diabetes mellitus, with the support of important associations such as the World Health Organisation (WHO) [3]. In contrast to blood glucose levels, the level of HbA1c is not affected by changes in lifestyle in the short term and shows much lower variability in multiple measurements in the same patient [4].

HbA1c is a glycated form of hemoglobin. It is formed by non-enzymatic covalent binding of glucose to hemoglobin. Various glycated hemoglobins are formed, of which HbA1c is a ketoamine species specifically derived from the nearly irreversible glycosylation of the N-terminal valine residues of two β chains [5]. The turnover of HbA1c is dependent on the life span of red blood cells, so it reflects blood sugar levels for the previous 90–120 days [5]. There are two principal methods for measuring HbA1c: separation and chemical. The separation methods enable the separation of fractions and their quantification, based on charge difference between HbA1c and non-glycated hemoglobin, which uses ion capillary electrophoresis and exchange chromatography or chemical traits such as affinity chromatography. The measurement of HbA1c by chemical methods is based on the chemical response of the glycated terminal of the β-chain, with parallel measurement of total hemoglobin levels. This concept is based on immunochemical and enzymatic assays. High performance liquid chromatography meets the requirements of functionality, quality and robustness [6]. Thus, most laboratories in the world, including Israel, measure HbA1c with this method.

POTENTIAL OBSTACLES TO HbA1c MEASUREMENTS
HbA1c levels are dependent on the life span of the erythrocyte and the rate of glycation. In clinical conditions character-
ized by a short erythrocyte life span or a low rate of glycation there will be underestimates of HbA1c levels. However, in conditions characterized by a longer erythrocyte life span or a high rate of glycation there will be overestimates of HbA1c [6]. Similarly, several medical conditions can affect the HbA1c measurement process itself [7]. The most common conditions that can affect HbA1c levels in the world are hemoglobinopathies and anemias [7]. However, there are many other clinical conditions that affect measurement results. The primary factors that can affect HbA1c levels are listed in Table 1. In addition to all the factors cited in the literature, there are ethnic-based factors that are not always addressed by clinicians but are gaining in recognition over time. In this article we reviewed the types of medical conditions in the Bedouin population that can affect HbA1c levels and the ways in which they are affected.

**HEMOGLOBINOPATHIES**

The term “hemoglobinopathy” encompasses all the genetic hemoglobin diseases. They can be categorized into two principal groups: thalassemia and structural hemoglobin variants. Both are caused by mutations/deletions in the α- or β-globin genes. When genetic impairments cause a problem in hemoglobin production, the result is thalassemia. The hemoglobin structure in these cases is normal. When the genetic defect causes a change in hemoglobin structure, the result is abnormal hemoglobin. Over 300 hemoglobin variants have been identified, with 99% of them being HbD, HbE, HbC, or HbS.

Hemoglobinopathies are generally seen in the Mediterranean area and large areas of Asia and Africa [8]. Thalassemia is common in several ethnic groups in Israel including Arabs [9]. Sickle cell anemia is found almost exclusively in the Arab sector in Israel [10]. The custom of consanguinity significantly increases the prevalence of recessive autosomal diseases such as hemoglobinopathies. Although the exact prevalence of hemoglobinopathies in the Bedouin population of southern Israel has not been investigated, the fact that 40% of the community are married to cousins and another 20% to more distant relatives [1] raises suspicion that this problem is much more prevalent in the Bedouin community than among other ethnic groups in Israel.

The epsilon gamma delta beta (εγδβ) thalassemias are very rare and sporadic conditions caused by a deletion of the β-globin gene cluster. This mutation, which is expressed by the longest deletion ever reported, was described in 12 relatives from the same Bedouin tribe in southern Israel [11]. Congenital dyserythropoietic anemia (CDA) type I is a rare idiopathic macrocytic anemia. It is characterized by thalassemia-like features. This rare anemia has been described in 20 relatives in a Bedouin tribe in Israel [12]. They presented

**Multiple medical conditions exist in the Bedouin population and among populations with similar characteristics that can affect HbA1c measurement**

with high levels of hemoglobin A2 or a high ratio of alpha to non-alpha globin. HbA2 and HbF do not have β-chains and their rate of glycation is about a third of HbA. The production of β-chains is delayed in β-thalassemia and the level of HbF that does not contain β-chains is increased by a compensatory mechanism [6]. Thus, patients with thalassemia beta and thalassemia-like diseases that impair the production of β-chains can have underestimated HbA1c levels. In cases of major thalassemia the effect of the reduced amount of β-chains is additive with the reducing effect of hemolysis on erythrocyte life span to further decrease the value of HbA1c. Patients who require blood transfusions because of thalassemia will also have underestimates of HbA1c for the same reason.

In the case of hemoglobin variants of the most common types (S, C, E, D) [9], the change in amino acids causes a change in the net charge that affects the measurement of HbA1c by methods based on charge difference, such as ion exchange chromatography. This leads to a condition in which hemoglobin variants, both glycated and non-glycated, co-elute or co-migrate with HbA1C causing an overestimate of

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**Table 1. Common factors that affect HbA1c measurements**

<table>
<thead>
<tr>
<th>Conditions leading to increased HbA1c levels</th>
<th>Conditions leading to decreased HbA1c levels</th>
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</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>Hemolytic anemias of various causes</td>
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<tr>
<td>Vitamin B12-deficiency anemia</td>
<td>Heterozygous thalassemia</td>
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<tr>
<td>Spleenectomy</td>
<td>Erythropoietin supplementation</td>
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<td>Chronic renal failure</td>
<td>Iron supplementation</td>
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<td>Alcoholism</td>
<td>Vitamin B12 supplementation</td>
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<td>Hyperbilirubinemia</td>
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<td>Chronic opiate use</td>
<td>Vitamin C</td>
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<td>Vitamin E</td>
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<td>Selenomegaly</td>
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<td>Antiretroviral drugs</td>
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<td>Hypertriglyceridemia</td>
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</tbody>
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**Figure 1. Glycation of hemoglobin**

- HCOH + HbN-protein → rapid HCOH + N-protein
- HCOH + HbN-protein → slow HCOH + N-protein
- C + O
- Adenine rearrangement
- Glucose
- Ketoamine (Schiff base)

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HbA1c [13]. With the HPLC measurement method, there are chromatographic peaks that make interpretation of the result difficult. Modern analyzers can identify and even characterize the presence of clinically silent hemoglobin variants by abnormal peaks on the chromatogram. Previous generation analyzers do not have the resolution needed for this. However, homozygosity for HbS, HbC, HbD, or sickle-hemoglobin C disease (HbSC) can cause hemolytic anemia that reduces HbA1c levels [14]. Many studies have shown that in cases of heterozygosity for hemoglobin variants, ion exchange chromatography is not affected and there is no statistically significant change in HbA1c levels [15].

IRON DEFICIENCY ANEMIA
Iron deficiency anemia (IDA) is a worldwide problem. According to a WHO report Israel, like most other developed countries, is considered to have a mild to moderate anemia problem with a prevalence rate below 19% [16]. However, this report did not look at ethnic differences. Many of the characteristics of the Bedouin population in southern Israel, such as low socio-economic status and high birth rates are risk factors for IDA. A high rate of infectious diseases and intestinal parasites are additional risk factors [1]. The results of a study that compared anemia between Bedouin and Jewish women of childbearing age showed that more Bedouin women present with severe anemia, defined as hemoglobin below 8 g/dl [17].

In recent years there have been reports that patients with IDA have overestimates of HbA1c levels [18,19] and this is directly related to the severity of the anemia [18]. There are two putative mechanisms for the effect of IDA on HbA1c. The first is that malondialdehyde whose level is increased in patients with IDA [20] may increase the rate of hemoglobin glycation [21]. The other is the prolongation of the erythrocyte life span because new erythrocyte production is impaired in IDA, leading to increased levels of HbA1c [22].

VITAMIN B12-DEFICIENCY ANEMIA
Meat is the primary source of vitamin B12 [23]. Poverty, with its incumbent low intake of meat, is a risk factor for vitamin B12 deficiency anemia. As mentioned above, the Bedouin community in southern Israel is at the bottom of the socioeconomic scale in Israel. In addition, the custom of consanguinity increases the percentage of clinical conditions of malabsorption even among those who eat enough meat. Some of these conditions are the result of diagnosed diseases [24] while others are unexplained [23]. Vitamin B12 deficiency can cause megaloblastic anemia with impaired production of new erythrocytes and increased life span of existing erythrocytes with a consequent overestimation of HbA1c levels.

HYPERBILIRUBINEMIA
We discussed the high prevalence of hemolytic diseases such as thalassemia in the Bedouin population. These diseases can cause indirect hyperbilirubinemia. Furthermore, Gilbert’s disease (benign unconjugated hyperbilirubinemia) can be a source of hyperbilirubinemia in this population. Like any other autosomal recessive disease its prevalence increases in populations characterized by consanguinity [25]. G6PD is more prevalent in the Arab population than in the Jewish population in Israel [26]. The combination of Gilbert’s syndrome with thalassemia or G6PD can cause severe hyperbilirubinemia [27,28]. Hyperbilirubinemia resulting from Gilbert’s syndrome or G6PD can be exacerbated by the fast of Ramadan. The Bedouins in Israel are a traditional Muslim community that adheres to this fast for a month from sunrise to sunset every year [29]. Hyperbilirubinemia can lead to overestimates of HbA1c levels when measured by the charge separation method. Bilirubin migrates with the fast hemoglobin and absorbs at the detecting wavelength [13].

PREGNANCY
The Bedouin sector is characterized by a high birth rate with one of the highest rates of natural population increase in the world [1]. Pregnancy is associated with a significant drop in HbA1c and there is consistent evidence that pregnant women (with and without diabetes mellitus) have low rates of HbA1c compared to non-pregnant women. The possible explanations for this finding are a drop in fasting blood glucose in pregnancy and a shorter erythrocyte life span [30]. In late pregnancy HbA1c levels usually rise by 0.1–0.2% [31].

Applying an HbA1C threshold of 6.5% to women with a diagnosis of diabetes before 20 weeks of pregnancy by an oral glucose tolerance test (OGTT) would miss almost half of the cases. A recent review recommends an HbA1C level of 5.9% to detect diabetes in early pregnancy [31]. An HbA1C level > 6%, measured in late pregnancy, has a high specificity for gestational diabetes mellitus [31]. Thus, although HbA1C was endorsed as a potential screening and monitoring tool for gestational diabetes mellitus or preexisting diabetes mellitus in pregnancy, a non-pregnancy threshold cannot be applied for these purposes.

RENAI FAILURE
Renal failure is the primary cause of morbidity and mortality in patients with diabetes mellitus, and the condition is the leading cause of renal failure throughout the world. According to a recent update [4] the age-adjusted prevalence of diabetes mellitus is 12.3% in the Bedouin population versus 8.2% in the non-Arab population in southern Israel. Thus, it is reasonable to assume that the prevalence of renal failure is higher in
the Bedouin sector than in the general population of Israel. The life span of erythrocytes is abbreviated in renal failure patients, and in patients with end-stage renal failure there is the additional effect of hemodialysis that shortens the life span of erythrocytes even further. Therefore, the value of HbA1c will be underestimated. However, there are several additional factors that could work in the opposite direction and raise the level of HbA1c [32]. The level of carbamylated hemoglobin (carbamyl-Hb) is increased in patients with uremia. Carbamyl-Hb has an isoelectric point similar to that of HbA1c and can therefore interfere with charge-based methods by co-eluting with HbA1c and causing a false overestimation of HbA1c [32].

A reduced level of erythropoietin that can cause a prolongation of the life span of existing erythrocytes, an increase in the rate of glycation, and exposure to high concentrations of glucose during dialysis are additional factors that can lead to an overestimation of HbA1c. In general, HbA1c levels tend to be lower in renal failure patients [32].

ETHNICITY AND AGE

Differences in HbA1c levels among populations of different ethnic and racial origins have been recognized for years but were usually attributed to differences in the availability and quality of healthcare services. Recently, there has been a growing body of evidence that HbA1c levels are higher by a mean of 0.1–0.4% for healthy Hispanic, African-American, and Asian children and adults as well as members of these groups with pre-diabetes and diabetes mellitus compared to white individuals with the same mean blood glucose level and the same results in glucose tolerance tests [13,33]. In recent years original studies and a large meta-analysis in Arab populations have shown lower HbA1c levels for the same blood glucose levels than in European populations, with a lower sensitivity rate for the diagnosis of diabetes mellitus in Arab populations compared to other populations in the world [34,35]. Possible explanations for these findings include differences in erythrocyte survival, differences in the internal and external cellular environment, and the genetic background for glycation rate.

Older patients have higher values of HbA1c than younger ones and there appears to be an increase of 0.6% in mean HbA1c between the ages of 40–70 years [13]. The Muslim Bedouin population is a young one with a median age of 12.7 years compared to 18.7 for all Muslim populations and 28.6 for the overall population in Israel [1]. Diabetes mellitus at a relatively young age (40–49 years) is three times more common in the Bedouin sector compared to the Jewish population [2]. Thus, there are many more relatively young diabetes mellitus patients among Bedouins compared to the Jewish population.

Age-dependent differences for glycated hemoglobin should be considered when interpreting the results of laboratory tests. The characteristics of morbidity in the Bedouin sector, the effect of HbA1c values, and possible explanations for this effect are summarized in Table 2.

POSSIBLE ALTERNATIVES TO HbA1c

In cases where HbA1c measurements are not reliable, other measures of chronic glycaemia can be used. Blood proteins also undergo glycation so the main candidate measurement that have been used are fructosamine and glycated albumin. Another potential candidate is 1,5-anhydroglucitol (1,5-AG). Fructosamine refers to total glycated serum protein (in particular albumin, but also immunoglobulins and other blood proteins) while glycated albumin, which comprises 80% of the total glycations in plasma, is measured as part of total albumin [36]. The half-life of albumin and other blood proteins

<table>
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<tr>
<th>Characteristic</th>
<th>Type of Interference</th>
<th>Possible explanation</th>
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<tbody>
<tr>
<td>Thalassemia traits</td>
<td>Underestimate</td>
<td>Decreased glycation</td>
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<tr>
<td>Homozygous thalassemia</td>
<td>Underestimate</td>
<td>Hemolysis</td>
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<td>Homozygous hemoglobin variants</td>
<td>Overestimate or</td>
<td>Abnormal co-eluted peaks on chromatograms</td>
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<tr>
<td></td>
<td>Underestimate</td>
<td>Hemolysis</td>
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<tr>
<td>Heterozygous hemoglobin variants</td>
<td>No interference</td>
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<tr>
<td>Congenital dyserythropoietic</td>
<td>Underestimate</td>
<td>Thalassemia-like features, high alpha to non-alpha globin ratio, increased glycation</td>
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<td>anaemia type 1</td>
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<tr>
<td>Iron deficiency anaemia</td>
<td>Overestimate</td>
<td>Increased erythrocyte life span and increased glycation</td>
</tr>
<tr>
<td>B-12 deficiency anaemia</td>
<td>Overestimate</td>
<td>Increased erythrocyte life span</td>
</tr>
<tr>
<td>Treatment for iron deficiency</td>
<td>Underestimate</td>
<td>Decreases erythrocyte life span</td>
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<td>and B12-deficiency anaemia</td>
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<td>Gilbert's disease</td>
<td>Overestimate</td>
<td>Bilirubin migrates with fast hemoglobin and absorbs at the detecting wavelength</td>
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<tr>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>Overestimate</td>
<td>Bilirubin migrates with fast hemoglobin and absorbs at the detecting wavelength</td>
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<tr>
<td>Pregnancy, first two trimesters</td>
<td>Underestimate</td>
<td>Decreased fasting blood glucose, decreased erythrocyte life span</td>
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<tr>
<td>Pregnancy, last trimester</td>
<td>Inconsistent in</td>
<td>Iron deficiency anaemia? Hemodilution? Increased red cell turnover?</td>
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<td>different studies</td>
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<tr>
<td>Chronic renal failure</td>
<td>Usually underestimation, but also</td>
<td>Decreased erythrocyte life span</td>
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<td>Overestimation</td>
<td>Increased erythrocyte life span</td>
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<tr>
<td>Arab ethnicity</td>
<td>Decrease</td>
<td>Ethnic differences in red cell survival, glycation rate</td>
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<tr>
<td>Young population</td>
<td>Decrease</td>
<td>Glycation rate</td>
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proteins is much shorter than that of erythrocytes, so measurement of fructosamine and glycated albumin reflect mean glycemia over the previous 2 to 3 weeks. 1,5-AG, a 6-carbon monosaccharide, which comes primarily from the diet, reflects mean glycemia over the previous 2–14 days. When blood glucose is high it competes with 1,5-AG for reabsorption, 1,5-AG is secreted in the urine and its concentration in blood decreases. Soybeans, beef, rice, and bread contain large quantities of 1,5-AG and complicate interpretation of the test. Fructosamine and glycated albumin are well-correlated with fasting glucose and HbA1c. There is evidence that the precision of these markers as screening and diagnostic tests for diabetes mellitus and as a monitoring tool for previously diagnosed diabetes mellitus is even better than HbA1c [36,37]. Glycated albumin was found to be effective in the prediction of ischemic heart disease with a better diagnostic performance than HbA1c [38]. However, clinical conditions that have a negative effect on protein turnover can also affect the concentration of glycated proteins. These include conditions such as nephrotic syndrome, liver cirrhosis, and thyroid disease. Glycated albumin levels are usually expressed as a percentage of total albumin, while fructosamine levels are not generally adjusted for either albumin or total protein concentrations. Thus, diseases that are associated with hypoproteinemia will affect the level of fructosamine more than glycated albumin. Immunoglobulin levels, especially IgA, that vary in different clinical conditions also affect fructosamine values more than glycated albumin. In light of the higher sensitivity and precision of glycated albumin it is the test of choice over fructosamine [39]. There are many methods to measure glycated albumin including boronate affinity chromatography, ion exchange chromatography, high performance liquid chromatography, and immunoassays [37].

IMPLEMENTATION OF ALTERNATIVE MEASURES TO DIAGNOSE AND MONITOR DIABETES MELLITUS IN THE BEDOUIN SECTOR

We described clinical conditions that affect the reliability of HbA1c measurements and are common in the Muslim Bedouin community in Israel. In conditions that affect the half-life, the structure, and chemical characteristics of hemoglobin, fructosamine, and glycated albumin can be appropriate and reliable alternatives. Not all HbA1c measurement methods are affected by abnormal hemoglobin, and some of the new HPLC-based instruments can differentiate between HbA1c and hemoglobin and abnormal hemoglobin variants. Glycated albumin is less affected than HbA1c and fructosamine during pregnancy. The more dynamic changes in glycated albumin values due to the short half-life can serve to monitor diabetes mellitus in pregnancy, including gestational diabetes and other conditions in which it is important to know the degree of glucose control in the short term [39]. Several studies have shown that glycated albumin is a more precise test for assessing glycemia in patients with renal failure, and even in early stages of dialysis, when the precision of HbA1c and fructosamine decrease [37].

CONCLUSIONS

Diabetes mellitus is very common and presents at a younger age in the Bedouin sector in southern Israel. Early detection and strict control are critical for the prevention of complications and mortality. While HbA1c is the accepted standard for the diagnosis and monitoring of diabetes mellitus, in this specific community the unique customs, the genetic background, and unique morbidity can lead to overestimation or underestimation of HbA1c values in patients with the described conditions. Healthcare providers who work with this population, or with similar populations around the world, should recognize that the interpretation of test results can be problematic in these patients. They should be familiar with and use other markers to diagnose and monitor diabetes mellitus. Diabetic patients suffering from those conditions should be educated regarding the alternative ways of monitoring their disease [40].

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References


Peripheral TREM1 responses to brain and intestinal immunogens amplify stroke severity

Stroke is a multiphasic process in which initial cerebral ischemia is followed by secondary injury from immune responses to ischemic brain components. Liu et al. demonstrated that peripheral CD11b+CD45+ myeloid cells magnify stroke injury via activation of receptor expressed on myeloid cells (TREM1), an amplifier of proinflammatory innate immune responses. TREM1 was induced within hours after stroke peripherally in CD11b+CD45+ cells trafficking to ischemic brain. TREM1 inhibition genetically or pharmacologically improved outcome via protective antioxidant and anti-inflammatory mechanisms. Positron electron tomography imaging using radiolabeled antibody recognizing TREM1 revealed elevated TREM1 expression in spleen and, unexpectedly, in intestine. In the lamina propria, noradrenergic-dependent increases in gut permeability induced TREM1 on inflammatory Ly6C+MHCII+ macrophages, further increasing epithelial permeability and facilitating bacterial translocation across the gut barrier. Thus, following stroke, peripheral TREM1 induction amplifies proinflammatory responses to both brain-derived and intestinal-derived immunogenic components. Critically, targeting this specific innate immune pathway reduces cerebral injury.

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Eitan Israeli

"Everyone discurses my art and pretends to understand, as if it were necessary to understand, when it is simply necessary to love"

Claude Monet (1840–1926), painter