Glycated Hemoglobin in Non-diabetic Hypothyroid Patients

Thesis for the partial fulfillment of Masters Degree of Internal Medicine

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Finally, I appreciate the cooperation of our dear patients, I hope this work offers a chance for a better state of health which they deserve after their long pains and suffering.
Abstract

- **Background**: Hypothyroidism is a prevalent disease mostly affecting middle aged women. Recently, the American Diabetes Association ADA has announced the use of glycated hemoglobin more than 6.5% for the diagnosis of diabetes mellitus. On the other hand, recent reports have stated a spuriously high level of glycated hemoglobin in non diabetic hypothyroid patients. Furthermore, conflicting results of the relation of (GA) glycated albumin (as an alternative to HbA1c) to hypothyroidism was found in several recent studies.

- **Objectives**: Assess the HbA1c level in non diabetic hypothyroid patient and assess glycated albumin (fructosamine) as an alternative to it.

- **Methods**: 96 hypothyroid non-diabetic patients was assessed for HBA1c and fructosamine. These levels was compared to 96 controls, who are non diabetic non hypothyroid patients. Full clinical examination and history will be performed for the patients and controls. The following labs was performed for all subjects: Blood glucose level, Hemoglobin, Thyroid functions was also performed. Glycated hemoglobin (HBA1c), was done as well as fructoseamine for all candidates.

- **Results**: HbA1c levels increases in non diabetic hypothyroid patients. There is a significant positive correlation between HbA1c and TSH. There was no significant correlation between fructosamine and thyroid function.

- **Conclusion**: HbA1c levels increases in non diabetic hypothyroid patients. Because our study found positive correlation between fructosamine and free T4, we do not recommend it as an alternative to HbA1c for diagnosis of diabetes. Hence fasting and post prandial
blood sugar are recommended for diagnosis and follow up of diabetes mellitus in hypothyroid patients.

- **Keywords:**
  (Hypothyroid, Fructosamine, Hemoglobin A1c, Non-diabetic).
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1,5-AG: 1,5-anhydroglucitol.
2hrs-pp: 2 hours post prandial.
ADAG: A1c-derived average glucose.
ANOVA: analysis of variance.
Anti-TSH MAb: anti thyroid-stimulating hormone Monoclonal antibodies.
Anti-TSH-HRP: anti thyroid-stimulating hormone horseradish peroxidase.
CBI TSH: Calbiotech thyroid-stimulating hormone.
D3: type 3 deiodinase.
DCCT: Diabetes Control and Complications Trial.
eAG: estimated average glucose.
EASD: European Association for the Study of Diabetes.
ELISA: Enzyme-Linked Immunosorbent Assay.
FBS: fasting blood sugar.
FPG: fasting plasma glucose.
FT3: Free triiodothyronine.
FT4: free thyroxine.
G\text{\textsubscript{s}}: stimulatory G protein.
HB: Hemoglobin.
HbA1c: hemoglobin A1c (glycated hemoglobin).
HOMA-IR: homeostasis model assessment–insulin resistance.
HPLC-CE: High-performance liquid chromatography - Capillary Electrophoresis.
HPLC-MS: High-performance liquid chromatography Mass Spectrometry.
HPLC: High-performance liquid chromatography.
I\textsuperscript{123}: radioactive isotope of iodine.
IDF: International Diabetes Federation (IDF).
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>IFCC</td>
<td>International Federation of Clinical Chemistry.</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging.</td>
</tr>
<tr>
<td>NBT</td>
<td>nitrotetrazolium-blue.</td>
</tr>
<tr>
<td>NGSP</td>
<td>National Glycohemoglobin Standardization Program.</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey 3 (NHANES-3)</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence.</td>
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<tr>
<td>NIS</td>
<td>natriuric-iodide symporter.</td>
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<tr>
<td>OGTT</td>
<td>oral glucose tolerance test.</td>
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<td>POCT</td>
<td>point of care testing.</td>
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<tr>
<td>RBC</td>
<td>red blood cell.</td>
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<tr>
<td>rT3</td>
<td>reverse triiodothyronine.</td>
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<tr>
<td>SIGT</td>
<td>Screening for Impaired Glucose Tolerance</td>
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<td>TBG</td>
<td>thyroxine-binding globulin.</td>
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<tr>
<td>Tg-Ab</td>
<td>anti-thyroglobulin antibody.</td>
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<tr>
<td>THW</td>
<td>thyroid hormone withdrawal.</td>
</tr>
<tr>
<td>TMB</td>
<td>3, 3’,5,5’-Tetramethylbenzidine.</td>
</tr>
<tr>
<td>TPO-Ab</td>
<td>thyroid peroxidase antibodies.</td>
</tr>
<tr>
<td>TRH</td>
<td>thyrotropin-releasing hormone.</td>
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<tr>
<td>TSH</td>
<td>thyroid-stimulating hormone.</td>
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</tbody>
</table>
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Introduction

Hypothyroidism is a prevalent disease mostly affecting middle aged women reaching a prevalence of 1.5 million individuals in the US alone. In an Egyptian study, maternal hypothyroidism reached a significantly high number of 15% in that category alone.

Recently, the American Diabetes Association ADA has announced the use of glycated hemoglobin more than 6.5% for the diagnosis of diabetes mellitus. On the other hand, recent reports have stated a spuriously high level of glycated hemoglobin in non diabetic hypothyroid patients; Other studies stated the presence of a state of glucose intolerance in hypothyroid patients.

Furthermore, conflicting results of the relation of glycated albumin (as an alternative to HBA1c) to hypothyroidism was found in several recent studies. Thus a need for other more specific criteria for diagnosis and follow up of diabetes, in hypothyroid patients.

Moreover, these recent studies were done on a small number of patients and used certain extreme overt hypothyroid states e.g. post surgical excision or pre irradiation. Furthermore, assessment of fructosamine as an alternative to glycated hemoglobin was not studied in hypothyroid patients.

Aim of work:

Assess HbA1c level in non diabetic hypothyroid patients and assess glycated albumin (fructosamine) as an alternative to it.
Chapter 1: Hemoglobin A1c

Definition:

Glycated hemoglobin (hemoglobin A1c, HbA1c, A1C, or Hb1c; sometimes also HbA1c) is a form of hemoglobin which is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement. The 2010 American Diabetes Association Standards of Medical Care in Diabetes added the A1c ≥ 48 mmol/mol (≥6.5%) as another criterion for the diagnosis of diabetes.\[1\]

Current concept of hemoglobin A1c:

Hemoglobin A1c, the most abundant minor hemoglobin component in human erythrocytes, is formed by the condensation of glucose with the N-terminal amino groups of the beta-chains of hemoglobin A.\[2\] As erythrocyte lifespan is constant and erythrocyte are freely permeable to glucose. HbA1c is formed slowly and non enzymatically.\[3\] Its rate of formation is directly proportional to ambient glucose concentration. HbA1c provides a glycemic history of the previous 120 days.
Chapter 1: Hemoglobin A1c

Advantages of hemoglobin A1c for the Diagnosis of Diabetes

It is Convenient (may be drawn at any time). Also Less susceptible to short-term lifestyle modification and small intra-individual biologic variation. In addition HbA1c monitoring is a valuable indicator of longer-term control and stability of blood glucose that does not require additional self-care requirements or International assay standardization.\textsuperscript{[4]} Thus National standards recommend that children, young people and adults with Type 1 diabetes be offered HbA1c testing between 2 and 4 times per annum, with more frequent testing if there are concerns about poor control. \textsuperscript{[5]} NICE guidelines recommend HbA1c measurements between 2 and 6 monthly for people with Type 2 diabetes, depending on stability of blood glucose control and changes in medications. \textsuperscript{[6]}

A graph of glucose changes over 9 weeks. The glucose (green line) changes between 7-12. This results in an HbA1c level of 10% at the end of the 9 weeks (red line). Poorly controlled.

Here the glucose changes between 5-9. This results in an HbA1c level of 7% at the end of the 9 weeks. Well controlled.

Figure (1-1): shows a graph of glucose changes over 9 weeks in the form of fluctuation of HbA1c level.
Chapter 1: Hemoglobin A1c

Measurement of hemoglobin A1c level

Technique of assessment:

There are a number of techniques used to measure A1C. Laboratories use:

- High-performance liquid chromatography (HPLC): The HbA1c result is calculated as a ratio to total haemoglobin by using a chromatogram.\[^7\]
- Immunoassay.

Point of care devices use:

- Immunoassay
- Boronate affinity chromatography\[^8\]

Devices that provide analyses at the point of care are now common place. Obtaining prompt results can increase clinical effectiveness and can contribute to improved outcomes for patients. The improved reliability and range of point of care testing (POCT) devices has led to their increased use in community clinics, general practitioner surgeries and the home environment.\[^9\]


Chapter 1: Hemoglobin A1c

Standardization & traceability:

HbA1c is now standardized & traceable to IFCC methods HPLC-CE & HPLC-MS. A new unit (mmol/mol) is used as part of this standardization. [10]

Switch to IFCC units:

The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and International Diabetes Federation (IDF) have agreed that, in the future, HbA1c is to be reported in the International Federation of Clinical Chemistry (IFCC) units. IFCC reporting was introduced in Europe except for the UK in 2003, and the UK has as of 1 June 2009 introduced dual reporting until 1 June 2011. [11]

The causes of switching to IFCC units are listed below according to: ADA, EASD, IFCC, IDF2007 Consensus [12]

(1) HbA1c test results should be standardized worldwide, including the reference system and results reporting.

(2) The new IFCC reference system is the only valid anchor to implement standardization of the HbA1c measurement.

(3) HbA1c results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation. [13]

(4) If the ongoing ‘average plasma glucose study’ fulfills its a priori specified criteria, an ADAG value calculated from the HbA1c result will also be reported as an interpretation of the HbA1c results.
Chapter 1: Hemoglobin A1c

(5) Glycaemic goals appearing in clinical guidelines should be expressed as IFCC units, derived NGSP units and as ADAG

Conversion between DCCT and IFCC is by the following equation:

\[
\text{IFCC-}HbA_{1c} (\text{mmol/mol}) = [\text{DCCT-}HbA_{1c} \; (\%) - 2.15] \times 10.929^{[14]}
\]

<table>
<thead>
<tr>
<th>IFCC-(HbA_{1c}) (mmol/mol)</th>
<th>DCCT-(HbA_{1c}) (%)</th>
<th>Mono S-(HbA_{1c}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
<td>20</td>
<td>4.0</td>
<td>2.9</td>
</tr>
<tr>
<td>30</td>
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<td>10.4</td>
<td>9.6</td>
</tr>
<tr>
<td>100</td>
<td>11.3</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Table (1-1): showing HbA1c represented in IFCC, DCCT and Mono-S (Swedish technique).

Interpretation of results:

Laboratory results may differ depending on the analytical technique, the age of the subject, and biological variation among individuals. In general, the reference range (that found in healthy persons), is about 20–40 mmol/mol (4%–5.9%).
Chapter 1: Hemoglobin A1c

**HbA1c in diabetes:**

Higher levels of HbA1c are found in people with persistently elevated blood sugar, as in diabetes mellitus. While diabetic patient treatment goals vary, many include a target range of HbA1c values. The International Diabetes Federation and American College of Endocrinology recommend HbA1c values below 48 mmol/mol (6.5%), while American Diabetes Association recommends that the HbA1c be below 53 mmol/mol (7.0%) for most patients.\(^{[15]}\)

A high HbA1c represents poor glucose control. However, a ‘good’ HbA1c in a patient with diabetes can still be riddled with a history of recent hypoglycemia, or even spikes of hyperglycemia. Regular blood glucose monitoring is still the best method for the analysis of overall vascular health with respect to blood sugar control.\(^{[15]}\)

Persistent elevations in blood sugar (and, therefore, HbA1c) increase the risk for the long-term vascular complications of diabetes such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy (loss of sensation, especially in the feet), gangrene, and gastroparesis (slowed emptying of the stomach). Poor blood glucose control also increases the risk of short-term complications of surgery such as poor wound healing.\(^{[16]}\)

The approximate mapping between HbA1c values given in DCCT percentage (%) and eAG (estimated average glucose) measurements is given by the following equation:

\[
eAG(\text{mg/dl}) = 28.7 \times \text{A1C} - 46.7 \\
eAG(\text{mmol/l}) = 1.59 \times \text{A1C} - 2.59
\]

Data in parentheses are 95% confidence intervals\(^{[17]}\).
Chapter 1: Hemoglobin A1c

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>eAG (estimated average glucose) mmol/mol</th>
<th>eAG (estimated average glucose) mmol/L</th>
<th>eAG (estimated average glucose) mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>31</td>
<td>5.4 (4.2–6.7)</td>
<td>97 (76–120)</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>7.0 (5.5–8.5)</td>
<td>126 (100–152)</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>8.6 (6.8–10.3)</td>
<td>154 (123–185)</td>
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<td>8</td>
<td>64</td>
<td>10.2 (8.1–12.1)</td>
<td>183 (147–217)</td>
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<td>75</td>
<td>11.8 (9.4–13.9)</td>
<td>212 (170–249)</td>
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<td>13.4 (10.7–15.7)</td>
<td>240 (193–282)</td>
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<td>97</td>
<td>14.9 (12.0–17.5)</td>
<td>269 (217–314)</td>
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<td>12</td>
<td>108</td>
<td>16.5 (13.3–19.3)</td>
<td>298 (240–347)</td>
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</tbody>
</table>

Table (1-2): showing values of HbA1c and eAG in different units.

**Modification by exercise training:**

A meta-analysis of research done to identify the effect of two different kinds of training programs (combined aerobic and eccentric resistance exercise program and aerobic exercise only) on the glycosylated hemoglobin levels of individuals with type 2 diabetes mellitus found that the effect of combining resistance exercise with aerobic exercise improved the glucose control more than just the aerobics alone. The average effect of the training programs included reductions of glycosylated hemoglobin of 9 mmol/mol (0.8 %), which was a result similar to that of long-term diet and drug. [18]