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Case Study

Effect of Hypothyroidism on HbA1C in Type 2 Diabetes patients: A Case Study

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Abstract

Incidence and prevalence of cardiometabolic diseases, have increased in the last four decades, to epidemic proportions worldwide. Despite a significant decline in the morbidity and mortality related, to cardiovascular diseases in industrialized nations, diabetes related deaths are on the rise. Patients with type-2 diabetes, suffer from a greater risk of vascular disease, often in association with dyslipidaemia. Majority of clinics, use fasting glucose or impaired glucose tolerance, to determine the progress of prediabetic state to that of diabetes. In view of the fact, that glycated haemoglobin A1c (HbA1c), represents three months average value of the glycemic load, it is used as the gold standard, to monitor the success or otherwise of the interventions, as well as progress or regression of the disease. Hypothyroidism causes many cardiometabolic abnormalities, as well as clinical symptoms, including insulin resistance, hypertension and dyslipidaemia, known features of type-2 diabetes. In this case report, we have presented our preliminary findings on, forty long-term diabetic subjects, less than 70 years of age and under regular supervised medical management. We have screened these patients, for vascular dysfunction using thermal imaging, to obtain risk scores for diabetes, hypertension and dyslipidaemia. Our study shows, that at clinically significant value of HbA1c (> 6.5), the observed values correlate well, with diabetes risk index. However, in some individuals with HbA1c greater than 9, the risk index is less than 3, indicating a moderate risk. In these patients, HbA1c seems to be independent of the state of diabetes condition, which is usually directly associated with HbA1c levels in type-2 diabetes. Results of these studies raise some very important questions on the role of glycemic load on treating diabetic patients with co-morbidities. What are the underlying mechanisms that promote vascular complications in diabetic patients with high levels of HbA1c? In the case of diabetic patients with comorbidities, is HbA1C sufficient for treatment? Further studies with a larger cohort, will provide answers to these very important questions related to the role of glycated proteins and lipids in the pathophysiology of endocrine disorders.

Keywords: *HbA1C; Diabetes; Hypothyroidism*

Introduction and Case Study

Cardiometabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes and vascular diseases are increased in prevalence and incidence in epidemic proportions worldwide [1-5]. Patients with type-2 diabetes suffer from a greater risk of vascular disease, often in association with dyslipidaemia.

Thyroid function might either contribute to these factors or make them worse [6]. Protein glycation is believed to be a spontaneous reaction that plays an important role in the pathogenesis of many endocrine disorders. The glycation of proteins is enhanced by elevated blood glucose levels. The major glycated protein of clinical importance in diabetic subjects is HbA1c. Increased glycated haemoglobin A1c have been documented in iron deficiency anaemic patients without any history of diabetes. Iodine deficiency disorder (IDD), is the most common endocrinopathy in the world and the most preventable cause of mental retardation [7,8]. Diet is the sole source of iodine and this micronutrient is crucial for the health and well-being of humans. Iodine is mostly concentrated in thyroid gland and deficiency of this

micronutrient in the diet results in hypothyroidism. Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose. It has been known for decades that thyroid hormones are important mediators of glucose homeostasis. Studies have demonstrated that diabetes and thyroid disorders tend to co-exist in patients. Both conditions involve a dysfunction of the endocrine system. A study in the Chinese population, found a higher TSH level in patients with metabolic syndrome compared to that in non-metabolic syndrome [8]. Iodine is essential for production of the thyroid hormones, thyroxine (T4) and triiodothyronine. Iodine deficiency may lead to goitre, hypothyroidism, poor growth and neurocognitive impairments [9].

Subclinical hypothyroidism even at level, defined as an elevated serum thyrotropin (thyroid stimulating hormone, TSH), with normal levels of free thyroxine (FT4) affects up to 10% of the adult population [10]. Hypothyroidism may be associated with an increased risk of heart failure and coronary artery disease events. Altered coagulation parameters, elevated lipoprotein (a) levels and low-grade inflammation are supposed to exist with the hypercholesterolemia of patients with hypothyroidism [11]. Studies have shown that regional cerebral blood flow and measures of regional metabolic activity, as measured by cerebral glucose metabolism, was generally decreased in hypothyroid patients [12]. Despite not knowing the underlying mechanism, it is speculated that b-cell dysfunction, insulin resistance and increased gluconeogenesis, with hepatic glucose production, occurs in hypothyroid individuals [13]. Hypothyroidism is associated with a faulty increase in HbA1c levels, reports Dr Vibhavasu Sharma in the Clinical Thyroidology for the Public (9.2. February 2016), published by the American Thyroid Association. In this report, he summarizes a study done in a hospital in India, which followed the effect of thyroid hormone treatment on pre-diabetes and management of diabetes. This study concluded that hypothyroidism may be falsely increasing the levels of the HbA1c. While thyroid hormone therapy decreased the HbA1c, suggesting an improvement of blood sugar control, actual measurements of blood sugars and overall glucose tolerance, were unchanged on thyroid hormone therapy. The authors conclude, 'that HbA1c is not a reliable diagnostic test for diabetes in the presence of hypothyroidism [14,15]. This 'special' condition, that occurs in hypothyroid patients, may lead to errors in diagnosing pre-diabetes and diabetes in patients with hypothyroidism. There is some speculation that the increased HbA1c in these conditions may reflect changes in red blood cell turnover [16].

Thyroid disorders, like diabetes are most common endocrine disorders worldwide [18]. Glycosylated glycation of valine in b-chain of haemoglobin forms glycosylated haemoglobin (HbA1c). Depletion of iron stores seems to elevate the rate of glycation of haemoglobin, independent of glucose levels [19]. Vascular endothelial dysfunction is supposed to be an important factor in the pathogenesis of microvascular and macrovascular complications in diabetes. Endothelial dysfunction, has also been described in hypothyroidism. In fact, hypothyroidism seems to increase the risk of vascular complications in type-2 diabetes. Egyptian researchers, have shown that SH group had a higher prevalence of dyslipidaemia, diabetic nephropathy, diabetic retinopathy, than the euthyroid group [20]. In our earlier articles, we have described a variety of methods, that are currently in use for monitoring altered blood flow, endothelial dysfunction and hardening of the arteries [21-26]. In our continuous efforts to develop simple non-invasive diagnostic tools, we have tested thermal imaging technology, to follow vascular dysfunction in diabetes subjects [25,26]. In this case study, we report some unique cases of hypothyroidism with high HbA1c with a low risk score of vascular abnormalities, associated with diabetes complications.

Discussion

At Aarca Research Pvt Ltd, Bengaluru, India, we use FLIR-E85 series thermal imaging camera, to obtain thermal scans of body surfaces for monitoring thermal variations. In a routine thermal imaging process, we shoot the video at 30 frames per second for one minute and capture 1800 frames of data. The data thus collected is computed and processed further, using a proprietary software, to obtain patterns of thermal variation and further graded for developing risk scores from 1 - 10, one being no risk and increases in the numbers indicating higher risk. These risk scores are developed individually for Diabetes, Hypertension and Dyslipidaemia based on the patterns which is serving as an indicative of vascular and hemodynamic changes. In an example, the diabetic, low-risk, individual (1a) is an 83 old male individual, for over half a century, with ten-year prediabetic condition and 20 years of well characterized diabetes, undergoing medical treatment which includes following medications: Metformin (2 gm), Glipizide (10 mg), Januvia (100 mg), Carvedilol (6.25 mg), Lisinopril

(20 mg) and Atorvastatin (10 mg). Mean interstitial glucose of this low-risk patient is 157 mg/dl, with a HbA1c of 7.2%, suggesting well controlled glucose metabolism. Risk score according to Aarca Research Product known as IHRA (Intelligent Health Risk Assessment) is for Diabetes (DM) 1.2, Hypertension (HTN) 2.9 and Lipids (LP) 2.7 on a scale of 1 - 10.

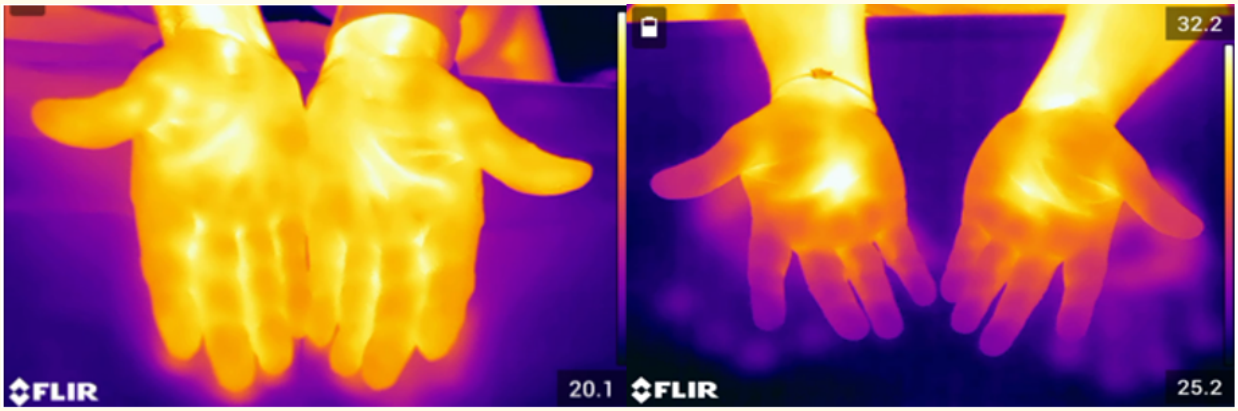

Figure 1a: *Low risk Patient*

Figure 1b: *Moderate-risk Patient*

In another example, the moderate-risk individual studied (B) is also a male, 65 years old with hypertension (7 years), type-2 diabetes (25 years; HbA1c: 6.5%), hyper thyroid condition (5 years) and a smoker (12 years). Medications include, Olsertain, Gucoril, Famcid, Thyrox, Moxavas, Ecospirin, Istamet, Trika, Remylein, Crevast and Mirtaz. Risk score for this individual from IHRA, is as follows: DM 4.2, HTN 3.5 and LP: 3.1. Despite robust management of the diabetes in the moderate-risk individual, we see early signs of vascular dysfunction as evidenced by the thermal asymmetry and higher risk scores compared with the low-risk individual. Because of this fact, the moderate-risk individual should be referred to the appropriate specialists for further interventions to restore the blood flow to the affected areas. Given that this technique can detect subtle alterations in blood flow to various regions of the human body we have extended our studies to screen diabetic subjects as well as patients with hypothyroidism (Figure 2).

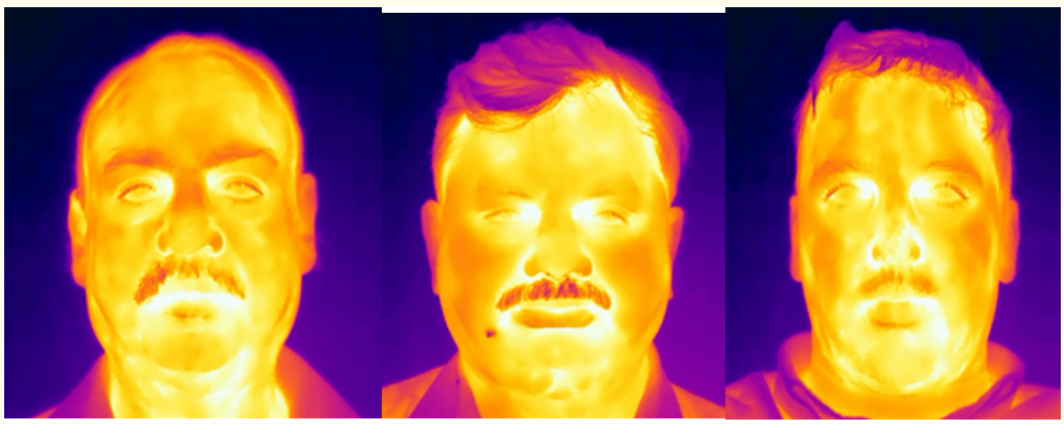

Figure 2: *Patient 1* *Patient 2* *Patient 3*

Thermal Images of the three patients screened for this case report.

All the three individuals selected for this case report, are male diabetic individuals. All are nonvegetarians. Medical history and clinical findings are presented in figure 3. Patient one is a long-term diabetic and the other two are recently diagnosed. Salient features of the blood chemistry are all the three had HbA1c above 11% (13.4, 11.4 and 11.5). As shown in figure 3 below, Subject 1 has no hypothyroid condition and thyroid levels are within normal range, whereas Subject 2 has elevate TSH levels indicating a hypothyroid condition and Subject 3 who is a known hypothyroid patient and taking medication, has elevated T4 levels. Aarca Research, IHRA score for diabetes risk index are 7.5, 3.8 and 0.5 and for Hypertension risk index are 1.6, 3.3 and 0.5 respectively.

Parameters	Subject 1	Subject 2	Subject 3
Age	56	53	42
Sex	Male	Male	Male
Food habits	Non-vegetarian	Non-vegetarian	Non-vegetarian
Diabetes Mellitus (DM)	Long term	Recent	Recent
DM Medication	Yes	Yes	Yes
Hypertension (HTN)	No	Recent	Long term
HTN Medication	No	Yes	Yes
Hypothyroid Condition	No	No	Yes
Hypothyroid Medication	No	No	Yes
Height (in inches)	164	158	166
Weight (in kgs)	77	74	113
Systolic	146	141	127
Diastolic	91	90	88
HbA1C	13.4	11.4	11.5
Total Cholesterol	194	209	191
HDL	28	35	44
LDL	105	152	123
Thioglycolates	301	116	114
T3	0.71	0.97	1
T4	7.97	6.34	12.89
TSH	3.14	7.2	1.55
Aarca Research Results			
DMI (Diabetes Risk Index)	7.5	3.8	0.9
HRI (Hypertension Risk Index)	1.6	3.3	0.5

Figure 3: *Medical history of the three patients studied.*

Patients (N = 40) whose data is presented in figure 4, are long-term diabetics, are less than 70 years of age and under regular supervised medical management. In this figure, we have highlighted the people with diabetes with hypothyroid as "X" and diabetic patient with no thyroid. As shown in the scatter graph, for a clinically significant value of HbA1c, i.e. 6.5 or greater, the HbA1c values are correlated well with the diabetes risk index (DRI) and patient biochemical data is indicating normal thyroid levels. However, in one segment of people with HbA1c > 9 and Aarca Research IHRA diabetes risk index is less than 3. It is observed that most of them have lower thyroid levels, indicating hypothyroid condition. In these patients, HbA1c values seem to be independent of the state of diabetes condition, which is usually directly associated with elevated HbA1c levels in type-2 diabetes patients. Some studies suggest that blood sugar metabolism may be affected in these subjects. It has been noted that patients who also have hypothyroidism, may have higher levels of HbA1c. It is very well known that factors other than glycemic status, can influence HbA1c levels, including altered red blood cell (RBC) turnover [16] and anaemia the common factors associated with hypothyroid condition [27].

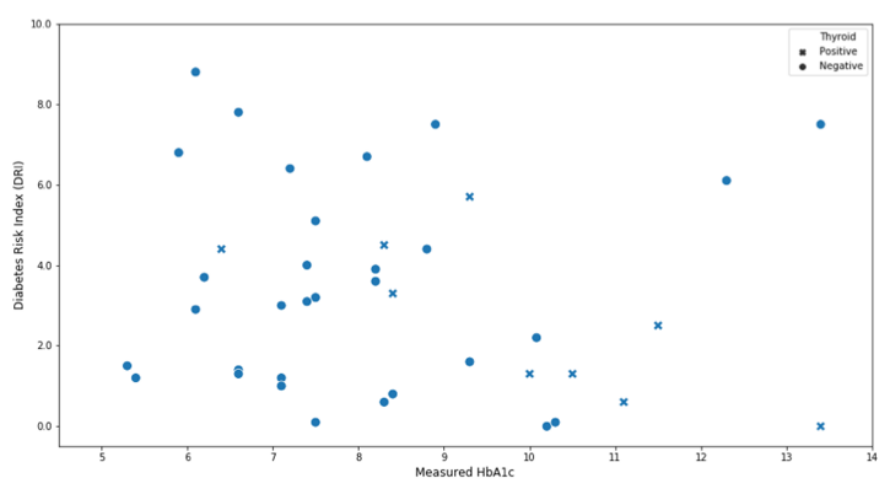

Figure 4: *Scatter graph of patient data on HbA1c plotted against diabetes risk index.*

Hypothyroidism causes many cardiometabolic abnormalities, as well as multiple clinical symptoms. Epidemiological studies have reported that association between hypothyroidism and dyslipidaemia increased the insulin resistance and risk of hypertension, increasing the risk for CVD events-known features of type-2 diabetes. Furthermore, these individuals are also exhibiting high HbA1c levels. Yet as we found in this study, their risk provided by Aarca Research product IHRA, for diabetes management and its related clinical complications is low to moderate. This also raises questions about the treatment plan for hyperglycaemia in these individuals and its effect on glucose metabolism [27,28] potentially making this as 'endocrinologists' nightmare. Recent meta-analysis of Thyroid Studies Collaboration concluded that hypothyroidism is a risk factor for ischemic heart disease (IHD) and cardiac mortality. Hypothyroidism is associated with higher risks of cardiac mortality and all-cause mortality compared with euthyroidism in the general public or in patients with cardiac disease.

In a recent overview in JAMA Network Open (2019), researchers discuss potential mechanisms, that may explain the complexity of this poorly understood endocrine disorder [30]. According to them, thyroid hormone is one of the key regulators of cardiac function and cardiovascular hemodynamics; therefore, inadequate thyroid hormone levels, impair the relaxation of vascular smooth muscle cells and decreases in cardiac contractility by regulating calcium uptake and the expression of several contractile proteins in cardiomyocytes. Low thyroid hormone levels, also increase systemic vascular resistance and induce endothelial dysfunction (vascular dysfunction), by reducing nitric oxide availability. Furthermore, NHANES study data has reported, that low thyroid function even with the normal range is associated with metabolic syndrome, owing to an increase in insulin resistance and might contribute to the progression of atherosclerosis and CVD risk [31] which is measured in Aarca Research thermal imaging technique indicated as risk score for diabetes management. Our thermal imaging studies show three patients with high HbA1c (greater than 11) had IHRA risk score for diabetes 7.5 (high) has no thyroid, 3.8 (moderate) has high TSH and 0.9 (low risk) a hypothyroid patient who is on medication. This technique which measures thermal variation based on vascular abnormality and hemodynamic changes, has a different risk index in all the three individuals despite having equivalent HbA1c levels.

Conclusion

We have presented clinical diagnosis, as well as the results of our novel thermal imaging data for three patients, with very high HbA1c values. In a group (n = 12) of long-term diabetic patients with relatively high HbA1c (greater than 9%) and IHRA low risk (< 3), we noted

that 9 people are suffering from hypothyroidism, a significant 75% of the sample size. From the preliminary studies we have done, it can be derived that HbA1c, the gold standard for glycemic load, is influenced in both the conditions. When all things being equal (age, family history, smoking history, etc) and if there are no existing comorbidities (hypertension, anemia), the IHRA risk index is in proportion to the HbA1c values. Since this technique measures the impact of functional and structural abnormalities and its impact on blood flow, the measured biomarkers indicate the impact of diabetes on the vascular structure, unlike the HbA1C which can be influenced by multiple factors. The results of these studies raise some very important questions on the role of glycemic load on treating diabetic patients with comorbidities. What are the underlying mechanisms that promote vascular complications in diabetics with high levels of HbA1c? In the case of diabetic patients with comorbidities, is HbA1C enough for treatment? The specific aims of our studies are to provide additional, relevant information, to the clinicians and medical practitioners so that they can assess the condition appropriately and recommend much-needed interventions and treatment plans, for diabetic patients with comorbidities.

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