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## CLINICAL PATHOLOGY

### HbA1c and Average Blood glucose

Verma Abhyuday, J. Muthukrishnan, KVS Harikumar, Modi K.D

HbA1c assay is the most widely accepted and reliable marker of chronic hyperglycemia as of today. Estimated average Glucose (eAG) level is derived from HbA1c by regression formula based on DCCT data. Self Monitoring of Blood Glucose (SMBG) is also now in vogue among diabetics. Comparisons are often done between average blood glucose (ABG) obtained through SMBG and eAG derived from HbA1c. It has been found recently that eAG is not a substitute for ABG derived from SMBG. Hence, a correction has been suggested in HbA1c derived eAG, based on a large clinical trial which correlates better with SMBG derived ABG.

#### Introduction

HbA1C assay is considered as a reliable and precise marker of assessing the status of diabetic control in patients. It has been popular for more than two decades for blood glucose monitoring. Landmark clinical trials have proved the merits of A1C monitoring for prevention of primary and secondary diabetic complications<sup>1</sup>. The positive correlation of A1C monitoring with diabetic complications shown in DCCT and UKPDS studies has made it a gold standard for monitoring therapeutic goal in diabetic. It helps in modifying the approach to the treatment of DM, and is a convincing tool to explain the importance of glycemic control in prevention of major DM complications.

#### Disadvantages of assessing HbA1C:

There are many factors that cause variation in A1C results. It does not reflect patterns of glycemic fluctuations, the effects of individual foods or exercise, or the immediate response to changes in therapy. Factors affecting A1C like erythrocyte turnover rate cause variation in results. Conditions that shorten erythrocyte life span, such as haemolytic anaemia or hypersplenism will decrease A1C. Conversely, diseases like aplastic anaemias, which results in aged red blood cells being in circulation associated with lack of new reticulocytes entering the pool, will cause A1C to progressively rise. Chemically modified haemoglobin, such as carbamylated haemoglobin associated with uraemia and acetylated haemoglobin formed after ingestion of large doses of salicylates, can falsely increase values. Kidney disease, liver disease, hemoglobinopathies, and recovery from blood loss will all decrease A1C. Vitamins C and E have been reported to lower A1C measurements, possibly by inhibiting glycation. Lower A1C levels are found in diabetic and non diabetic pregnant women, probably due both to lower fasting blood glucose and a shortened erythrocyte lifespan.<sup>6</sup> Iron-deficiency anaemia, has been associated with increased A1C. There is also some evidence of wide fluctuations in A1C between individuals

that are unrelated to glycemic status, suggesting that there are “low glycaters” and “high glycaters”. Different laboratories and methods used yield different A1C values. Many studies have shown that A1C is an index of average blood glucose over the preceding few weeks to months. A1C truly does not reflect glycemic control over last three months as claimed. Rather, it is weighted to more recent weeks. The average glycemia during the month preceding the A1C measurement contributes 50% of the result, during the 30-60 days prior to the A1C measurement contributes another 25%, and during the 60-120 days prior to the measurement contributes the final 25%. The fasting blood glucose as well as post meal glucose excursions contribute to HbA1c levels. Post meal blood glucose contributes significantly when A1C is <7.5%. On the other hand, fasting blood glucose contributes more when A1C is >7.5%. HbA1C, though a valuable parameter, is being expressed as percentage and patients and clinicians may perceive small changes as unimportant although they are linked to large health effects. The aforementioned reasons preclude the use of A1C per se for diagnosis of DM. So converting HbA1C to estimated average glucose (eAG) expressed in mmol/l or mg/dl will help in better understanding of the analytic changes. Other advantage of average blood glucose as seen in DCCT was that it was a predictor of the macro vascular complications of type 1 diabetes than HbA1c.

### **HbA1C derived Average blood glucose:**

Currently average blood glucose value (mg/dl or mmol/l) is derived from A1C report by a given formula based on DCCT data (average blood glucose (mg/dl) =  $(30.9 \times \text{HbA1C} (\%) - 60.6)$ ). However this A1C derived average blood glucose does not always correlate with clinical situation, it overestimates blood glucose levels. When a person achieves near normal glycemia as reflected by A1c value < 6% (eAG < 135mg/dl), he is more likely to develop episodes of hypoglycaemia. This was observed in DCCT trial also. Recently International Federation of Clinical Chemistry (IFCC) has developed a new calibration standard that gives approx. 1.5-2.0% lower values. Existing A1C assay represents mixture of multiple glycated haemoglobins (young less glycated and old erythrocytes). Instead of that IFCC has suggested measurement of one standard, only A1C measurement, to be expressed in mmol / mol. The advantage of the new value is that it reflects the actual blood glucose values but it has some disadvantages also. It is costly and needs re-education to patients and clinicians to avoid confusion. The relationship between A1C and blood glucose is complex. On average, A1C of 6% corresponds to mean blood glucose of 135 mg/dl. For every increase in A1C of 1%, mean blood glucose increases by 35mg/dl, Having lower average glucose at the same A1C may help explain why intensive DCCT treatment had increased incidence of hypoglycaemia and decreased microvascular complications compared with conventional treatment. Earlier few studies which tried to correlate A1C to average blood glucose (e.g. Svendsen et al 1982, Nathan et al 1983), suffered from relatively infrequent monitoring and small number of patients. DCCT has many shortcomings including small study population, homogenous cohort, infrequent measuring of capillary glucose and absence continuous blood glucose estimation. These infrequent glucose concentrations were not enough to compute a true ‘average’. Therefore despite our confidence in the ‘meaning’ of A1C assay according to DCCT the relationship between A1C and average glucose is not well established. (Table 1) Increasing awareness, frequent self monitoring of blood glucose (SMBG)

and availability of better, patient-friendly monitoring equipments that provide average blood glucose measures, has helped patient reach their glycemic control better. However, no formula-derived parameter can be better than real time SMBG derived average blood glucose, as reports are in same units as the patients' self monitoring of daily glycemia rather than as percent A1C. An alternate way to overcome this is to establish an exact relationship of the new results to average blood glucose. With a new reference range, new targets, and a new name, reporting chronic glycemia in same units as the patients' self monitoring of daily glycemia rather than as percent A1C, will be advantageous and will give a better understanding of glycemic control. In order to do this a reliable regression model is required. An international study was needed to establish the relationship between A1c- average glucose across diabetes type, races, and ethnicities, where a confirmed mathematical relationship can be reported in the same unit as patients' self monitoring of daily glycemia. On account of this correction, an international, multi-centric trial (A1c Derived Average Glucose (ADAG) study) with larger study population, different ethnic groups and heterogeneous patient groups (Type 1 DM, type 2 DM and non diabetic) were initiated and completed recently. The patients were subjected to frequent capillary blood glucose and continuous blood glucose estimations more frequently to establish the exact relationship between A1C and average blood glucose value This study showed a simple linear relationship between A1c level and average blood glucose with 90% of the estimated average glucose falling within + 15% range of regression line. Based on these findings, a new regression equation was derived, i.e. eAG (mg/dl) =28.7 X A1C – 46.7. The estimated average blood glucose value will be slightly lower than the present calculated value. This may explain why earlier patients with near normal HbA1C reported frequent hypoglycaemias.

## Conclusion

To conclude, calculating HbA1C has its own disadvantages. Currently used HbA1C derived average blood glucose according to DCCT trial overestimates blood glucose levels. The new formula by David M Nathan takes into consideration the mean value of multiple self-monitored blood glucose and hence is more representative of the actual mean blood glucose and claims a simple linear relationship between mean glucose and A1C levels. The reporting of the measured A1C as eAG, may now make a meaningful difference in setting up of treatment goals or adjusting treatment of diabetes mellitus.

**Table 1**

<b>HbA1c</b>	<b>Existing average glucose according to A1c mg/dl (mmol/L) (DCCT)</b>	<b>Proposed A1c derived Average Glucose mg/dl (mmol/L) (ADAG)</b>
5	100 (5.6)	96 (5.3)
6	135 (7.5)	125 (6.9)
7	170 (9.4)	153 (8.6)
8	205 (11.4)	184 (10.2)

9	240 (13.3)	214 (11.9)
10	275 (15.3)	243 (13.5)
11	310 (17.2)	273 (15.2)
12	345 (19.2)	303 (16.5)

### Existing and proposed A1C derived average blood glucose values

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## Low Ldl Cholesterol and Hscrp Achieves Best Cvd Risk Improvement

*MedWire News:* A subanalysis of data from the JUPITER trial shows that reduction in both low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein (hsCRP), obtained using rosuvastatin treatment, produces the optimum reduction in cardiovascular disease (CVD) risk.

The initial results from JUPITER showed that individuals with low to normal LDL cholesterol but raised hsCRP could benefit significantly from rosuvastatin treatment, as reported by *MedWire News*.

The results of this analysis, presented by Paul Ridker, Brigham and Women's Hospital in Boston, USA at the American College of Cardiology annual scientific sessions in Florida, Orlando, extend the original findings to show that asymptomatic individuals taking rosuvastatin for just under 2 years obtained the maximum benefit from the drug if they obtained both low hsCRP and LDL cholesterol levels. The findings are published simultaneously in *The Lancet*.

The researchers included data from 15,548 individuals (87% of original cohort) of whom 7832 were assigned to the placebo group and 7716 were assigned to take rosuvastatin 20 mg/day for a median period of 1.9 years.

Ridker and team prospectively assessed the effects of rosuvastatin on rates of nonfatal myocardial infarction, nonfatal stroke, and admission for unstable angina, arterial revascularisation, or cardiovascular death over the study period.

Despite the fact that levels of LDL cholesterol and hsCRP were only slightly correlated in individual patients, those who achieved a dual treatment target of LDL cholesterol lower than 1.8 mmol/l (70 mg/dl) and hsCRP lower than 2 mg/l had a 65% reduction in CVD events, compared with a 33% reduction in patients who achieved one or neither target.

They found that participants who achieved an LDL cholesterol level of below 1.8 mmol/l (70 mg/dl) had a 55% reduction in CVD events and those who achieved a hsCRP reduction of below 2 mg/l a 62% reduction.

Of note, patients who achieved the more stringent target of a LDL cholesterol level of below 1.8 mmol/l (70 mg/dl) and a hsCRP reduction of below 1 mg/l had a 79% reduction in CVD events.

“Despite the pathophysiologic evidence presented here, in low-risk primary prevention populations with raised LDL cholesterol or hsCRP, initial interventions should remain lifestyle recommendations for dietary restriction, exercise, and smoking cessation,” caution the authors.

“However, as our findings have shown, for people choosing to start pharmacologic prophylaxis, reductions in both LDL cholesterol and hsCRP are indicators of the success of treatment with statin therapy,” they conclude.

Jean-Pierre Després (Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec, Canada), author of an accompanying commentary, added: “These findings add to evidence that CVD has an inflammatory component and suggest that inflammation could become another target for primary prevention of cardiovascular disease.”

*Lancet 2009; Advance online publication*

## ANATOMIC PATHOLOGY

### **Multilayered Epithelium in Mucosal Biopsy Specimens from the Gastroesophageal Junction Region is a Histologic Marker of Gastroesophageal Reflux Disease**

**Glickman JN, Spechler SJ, Souza RF, Lunsford T, Lee E, Odze RD.**

Barrett esophagus (BE) is defined as a columnar metaplasia of the distal esophagus that develops as a result of chronic gastroesophageal reflux disease (GERD). A distinctive type of multilayered epithelium (ME) that exhibits features of both squamous and columnar epithelium has been hypothesized to represent an early, or intermediate, phase in the development of BE. The aim of this prospective study was to evaluate the prevalence and specificity of ME in mucosal biopsies of the squamocolumnar junction (SCJ) from patients who had GERD, either with or without BE. During endoscopic examination of the esophagus, 2 biopsy specimens were obtained from across the SCJ from 27 patients with BE, 12 patients who had GERD without BE, and 14 controls who had no symptoms or endoscopic or histologic signs of GERD. ME was present at the SCJ in 33%, 33%, and 0% of BE, GERD, and control patients, respectively. Compared with control subjects, the prevalence of ME was significantly higher in both GERD and BE patients ( $P < 0.05$ ).

In GERD patients without BE, ME was always detected adjacent to areas of cardia-type mucosa composed of mucous glands. ME from GERD patients and BE patients had a similar immunophenotype, showing expression of the intestinal markers MUC2 and cdx-2 in 38% and 77% of cases, respectively. The prevalence of expression of these markers in ME was significantly different from nongoblet epithelium in control patients. Our results provide further evidence that ME may represent an early, transitional form of columnar metaplasia, and that ME may be used as a histologic marker of reflux disease in mucosal biopsies from the gastroesophageal junction region.

*Am J Surg Pathol. 2009 Mar 17.*

## **Malacoplakia of the Tongue: A Case Report and Clinicopathologic Review of 6 Cases**

**Diapera MJ, Lozon CL, Thompson LD.**

**BACKGROUND:** Extra-urogenital tract malacoplakia is uncommon, with tongue malacoplakia being exceptionally rare. The nonspecific clinical presentation and variable histologic patterns can make recognition of this lesion and separation from other lesions challenging. There are only a few reported cases in the English literature.

**MATERIALS AND METHODS:** Five case reports of tongue malacoplakia were compiled from the literature (MedLine 1960-2008) and integrated with this case report.

**RESULTS:** The patients included 4 males and 2 females, ranging in age from 9 to 98 years (mean, 64 years). Patients presented with difficulty swallowing, foreign body sensation, a mass lesion, or referred pain (neck or ear). Symptoms were present from a few days up to 18 months. The base of the tongue was the most frequent site, although midline tongue and half of the tongue were also affected. Radiographic studies demonstrated a mass, with a single lesion showing positron emission tomography positivity. Two patients had previous cancers (prostate and colorectal; larynx). This case report was a farm hand for horses, with gram-negative rods, suggestive of *Rhodococcus equi* identified. The lesions were 1 to 2 cm in greatest dimension. Histologically, there is pseudoepitheliomatous hyperplasia or ulceration with a heavy acute and chronic inflammatory infiltrate. The subepithelial spaces are completely filled with eosinophilic histiocytes, most of which contain granular material in their cytoplasm. Well-formed, blue, calcific bodies are noted, a few showing a "targetoid appearance" and concentric lamination. These Michaelis-Gutmann bodies are positive with von Kossa, iron, and periodic acid-Schiff stains. These findings support a diagnosis of malacoplakia. The differential diagnosis includes granular cell tumor, poorly differentiated carcinoma, and Langerhans histiocytosis. Patients are managed with antibiotic therapy and excision.

CONCLUSIONS: Tongue malacoplakia is rare, often presenting as a mass lesion. Histologic recognition of this abnormal phagocytic disorder will prevent potentially disfiguring surgery.

*Am J Otolaryngol. 2009 Mar-Apr;30(2):101-5.*

## **Xanthogranulomatous Mastitis: Clinicopathology and Pathological Implications**

**Ja Seung Koo and Woohee Jung**

Xanthogranulomatous inflammation is an uncommon finding in the breast. Sixteen cases of xanthogranulomatous mastitis were reviewed to determine the characteristic clinicopathological features. Xanthogranulomatous mastitis involved foamy histiocyte clusters interspersed with inflammatory cells. Foamy histiocytes were bland with small pyknotic nuclei. Xanthogranulomatous mastitis was associated with fat necrosis in five cases (31%), multinucleated giant-cell reactions in six cases (38%), and cholesterol crystals in five cases (31%). In three cases (19%), xanthogranulomatous mastitis coincided with ductal carcinoma in situ or invasive ductal carcinoma. Duct ectasia with foamy histiocyte aggregates were noted in five cases (31%). It is suggested that the etiology of xanthogranulomatous mastitis is obstruction and rupture of the ectatic duct with foamy histiocyte aggregates. In breast core biopsy, granular cell tumor and invasive carcinoma such as histiocytoid carcinoma and lipid-rich carcinoma could demonstrate similar pathological features to xanthogranulomatous mastitis. In conclusion, xanthogranulomatous mastitis could be encountered in breast core biopsy and surgical excision tissue. Diagnosis of xanthogranulomatous mastitis can be made by excluding other diseases that elicit xanthogranulomatous inflammation in the breast. In breast core biopsy, xanthogranulomatous mastitis could be distinguished from granular cell tumor, histiocytoid carcinoma and lipid-rich carcinoma by using cytokeratin and histiocytic marker such as  $\alpha 1$ -anti-trypsin and CD68 stain.

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## **MICROBIOLOGY**

### **Mixed Infections of Helicobacter Pylori: Tissue Tropism and Histological Significance**

**S.-M. Sheu , B.-S. Sheu, C.-C. Lu, H.-B. Yang and J.-J. Wu**

Mixed infections with Helicobacter pylori facilitate interstrain gene transfer and the maintenance of genetic diversity for adaptation to the gastric environment, but whether mixed infections with histological significance and tissue tropism occur in the human stomach is still unclear.

*Helicobacter pylori* was isolated from the antrum and the corpus of 30 dyspeptic patients. Four to eight colonies were randomly collected from each site. The genetic diversity of each isolate was evaluated by comparing random amplified polymorphic DNA banding patterns. The prevalence of mixed infections was 23.3% (7/30), and different dominant strains were isolated from the antrum and the corpus specimens. In the 23 patients infected with a single strain, the acute inflammation (AI) score, chronic inflammation (CI) score, atrophy (AT) score and lymphoid follicle (LF) score of the antrum were usually higher than those of the corpus ( $p \leq 0.002$ ). However, in the seven patients with mixed infections, the CI, *H. pylori* density (HPD), AT and LF scores of the antrum and the corpus were similar ( $p > 0.05$ ). Moreover, the patients with mixed infections had marginally higher CI and HPD scores than those with single-strain infection ( $p = 0.062$  and  $p = 0.095$ , respectively) in the corpus and had a significantly higher rate of appearance of intestinal metaplasia (IM) in the antrum ( $p = 0.005$ ). These data show that *H. pylori* tissue tropism was found in the human stomach, and suggest that mixed infections could change the histological features in the antrum and in the corpus, and that they could be associated with the appearance of IM in the antrum.

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