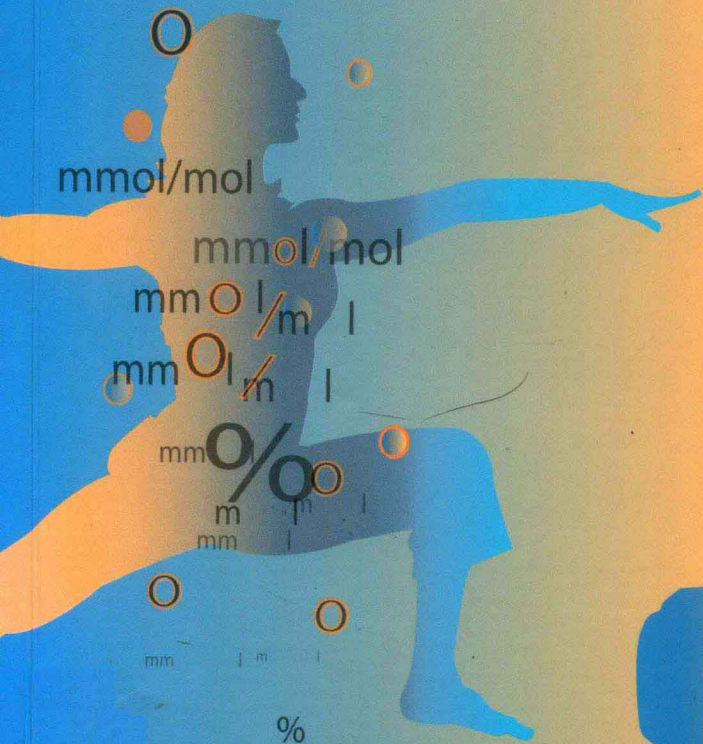
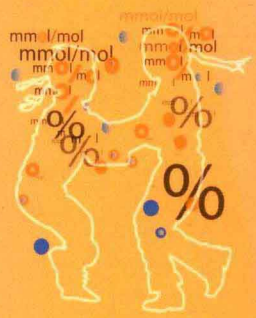
HbA_{1c} in Diabetes

case studies using IFCC units





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Diabetes UK

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Preface

The measurement of HbA_{1c} is a key tool in the treatment of diabetes mellitus. For health care professionals involved in the management of diabetes in the UK there is an additional complication, between 2009 and 2011, with a change of HbA_{1c} units. The old DCCT percentage is giving way to the internationally recognised IFCC units of mmol/mol in 2011.

To further the understanding of HbA_{1c} measurements, we have summarised the important issues and then appended a number of case studies involving a wide range of patients from children to the elderly, showing the measurements in both the 'old' and 'new' units. These cover a wide range of diabetes-related conditions and describe the treatment plans and follow-up. We hope that this book will be a useful resource for all those involved in diabetes care as they come to terms with IFCC reporting.

This cannot be the last word on the measurement or role of HbA_{1c} and we look forward to continuing the interaction with colleagues in the UK and further afield.

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Foreword

The relation of glycated haemoglobin to blood glucose levels was first discovered about 40 years ago. Over the next decade assays were developed to allow its routine use. It was a massive breakthrough for people with diabetes and health professionals, as for the first time there was an independent way of assessing average blood glucose levels over a period of several weeks. The test was first used for assessing control in 1976, and a wide range of different tests were developed. Some of these were cumbersome; many gave different values and it was not until the DCCT trial that an effort was made to standardise reporting. Since then, many laboratories worldwide align their results against the DCCT standard. The results have traditionally been presented as a percentage of total haemoglobin.

In the interim, the IFCC has developed a new standard and reference method against which other methods can be standardised, and absolute amounts of HbA_{1c} can be measured. As a result the recommendation now is that results should be presented as mmol glycated haemoglobin/mol unglycated haemoglobin. The UK is following this recommendation; parallel reporting is now in place and will continue until mid-2011. Obviously the numbers are different and it will take time for professionals and patients to attune themselves to the new units. This is of course not a new problem. Thirty-five years ago, most clinical biochemistry results were changed from a weight-based system to a molar system, and many analytes – including glucose – showed large changes in the actual numbers reported. The switch, backed by a strong educational program and initial double reporting, was relatively trouble-free.

The same should be true for HbA_{1c}. The current volume is an excellent adjunct to the educational process – and a novel and readable way of helping people. A series of case studies is presented, in which both ways of expressing HbA_{1c} are used. This covers a wide range of values and through repetition, the numbers start to become more familiar and make sense.

KGMM Alberti
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List of abbreviations

AA	Normal haemoglobin
AC	Haemoglobin C trait
ACB	Association for Clinical Biochemistry
ACD	Antihypertensive ACD algorithm
ACE	Angiotensin-converting enzyme
ACR	Albumin creatinine ratio
ACTH	Adrenocorticotropic hormone
AD	Haemoglobin D trait
ADA	American Diabetes Association
ADAG	A1C-derived average glucose
AE	Haemoglobin E trait
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Adrenergic receptor blocker
AS	Sickle cell trait
A1C	HbA_{1c}
BHS	British Hypertension Society
BM	Blood glucose strips
BMI	Body mass index
CGM	Continuous blood glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DIGAMI	Diabetes Mellitus, Insulin–Glucose Infusion in Acute Myocardial Infarction
DM	Diabetes mellitus
DUK	Diabetes UK
DVT	Deep vein thrombosis
eAG	Estimated average glucose
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
EDTA	Ethylenediamine tetraacetic acid
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GAD	Glutamic acid decarboxylase
GFH	Glucose Fructosamine HbA_{1c} (research study)

Hb	Haemoglobin
HbA_{1c}	Glycated haemoglobin
HbF	Fetal haemoglobin
HDL	High-density lipoprotein
HNF1A	Hepatic nuclear factor 1A
HPLC	High performance liquid chromatography
IDF	International Diabetes Foundation
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IFG	Impaired fasting glucose
IGF-1	Insulin-like growth factor 1
IGT	Impaired glucose tolerance
JDS	Japanese Diabetes Society
LDL	Low-density lipoprotein
LH	Luteinising hormone
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
NGSP	National Glycohemoglobin Standardization Program
NICE	National Institute for Health and Clinical Excellence
OGTT	Oral glucose tolerance test
PCI	Percutaneous coronary intervention (angioplasty)
POCT	Point of care testing
RPG	Random plasma glucose
SI	Système Internationale
SMBG	Self monitoring of blood glucose
SS	Sickle cell disease/anaemia
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
UKPDS	UK Prospective Diabetes Study
VA	Visual acuity
WHO	World Health Organisation
2hPG	2 hour plasma glucose
^{32}P	Radioactive isotope of phosphorus

Contents

Introduction

Background

What is diabetes?

Impairment of glucose regulation in the body leads to diabetes. In untreated diabetes, glucose levels in the blood increase. In type 1 diabetes, mainly found in children and young adults, β-cells in the islets of Langerhans of the pancreas fail to secrete insulin and insulin replacement is required.

In people with type 2 diabetes, typically diagnosed in middle age but now also in children, blood glucose levels rise as a result of both resistance to the action of insulin and also progressive β-cell dysfunction (Figure 1). In type 2 diabetes, treatment involves lifestyle changes and oral antidiabetes drugs that lead to an increase in insulin secretion from the pancreas or increased insulin sensitivity in the tissues. Injectable treatments may also be required, with the majority of people with type 2 diabetes ultimately requiring insulin.

Despite defects in the secretion and action of insulin being the cause of diabetes, the hormone is rarely measured in routine clinical care, although it can be measured easily on automated equipment in pathology laboratories. A reference method using mass spectrometry has been developed for calibration, so that in-

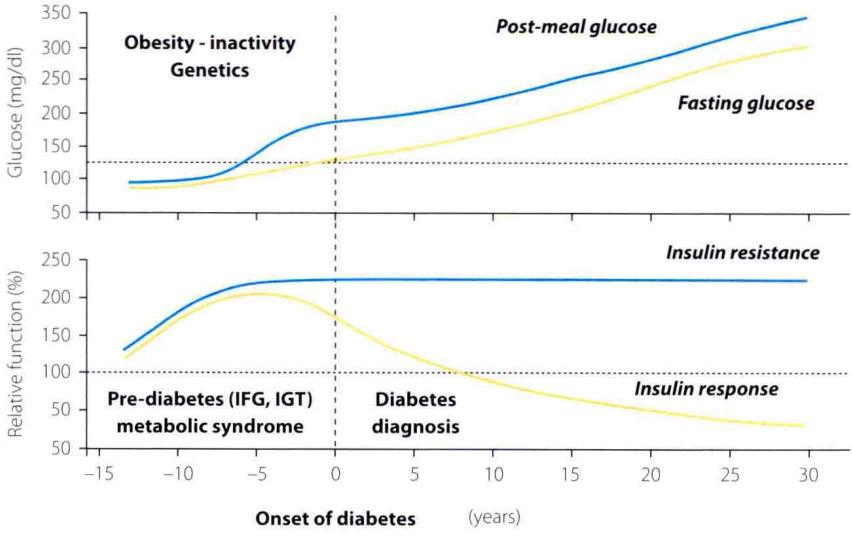

Figure 1 Development of type 2 diabetes over time.

sulin values obtained from different methods will be comparable. Blood glucose control is usually monitored in patients by determination of HbA_{1c} – a measure of glucose-bound (glycated) haemoglobin. This is proportional to the amount of glucose in the blood over the previous two to three months, the lifespan of red blood cells. Lowering blood glucose levels will lead to lower HbA_{1c} and failure to control blood glucose successfully, to high HbA_{1c}. Glycated haemoglobin has been used for assessing glycaemic control since 1976.

The prevalence of diabetes, particularly type 2, is increasing inexorably – putting a significant strain on healthcare resources that will impact most on developing regions of the world. Many of the ethnic groups that will be affected (e.g. those in India, China and Africa) are more susceptible to diabetes than Caucasians. Lifestyle is also a major factor: the likelihood of developing diabetes is increased when exercise levels are reduced and high calorific diets adopted, leading to overweight or obesity. These changes are typically related to urbanisation, industrialisation and the adoption of a western lifestyle.

The concentration of glucose in blood varies according to the time of the day and reflects the patient's nutritional intake and ability to metabolise glucose (Figure 2). In practice, blood is collected by health care professionals, with glucose measured at any time of the day (random plasma glucose, RPG), or at a pre-arranged time after fasting (fasting plasma glucose, FPG). Plasma glucose values are sometimes recorded at specified times, e.g. two hours after a meal or the time of the last meal is recorded.

Smaller differences occur in glucose levels when blood is obtained from various sites of the body or when different devices are used for measurement. Blood can be taken from veins (venous), finger pricks (capillary), the abdomen (interstitial) or arteries (arterial). To monitor their glucose control, patients may test their own blood using meters or implanted sensors. For medical review, they can have blood samples taken in a clinical setting, with measurement at point of care or in a central laboratory.

What is HbA_{1c}?

Glycation of haemoglobin is not catalysed by enzymes, but occurs through a chemical reaction that depends on the exposure of red blood cells to glucose circulating in the blood (Figure 3). Clinical management of diabetes involves regular measurement of HbA_{1c} to monitor the glucose level in the bloodstream. HbA_{1c} is usually measured at three- or six-monthly intervals or at the time of an annual review. One of the advantages of measuring HbA_{1c} rather than glucose is that fasting is not required. Although a venous blood sample is required routinely by most laboratories, HbA_{1c} can also be measured on capillary blood obtained from a finger prick, using smaller analysers located at point of care.

Any event or condition that affects haemoglobin, or red blood cells or their turnover may affect the amount of HbA_{1c} in circulating blood. Measurement of reticulocytes (immature red blood cells) will determine whether the turnover of red blood cells is affected; if it is accelerated, the reticulocyte count will be

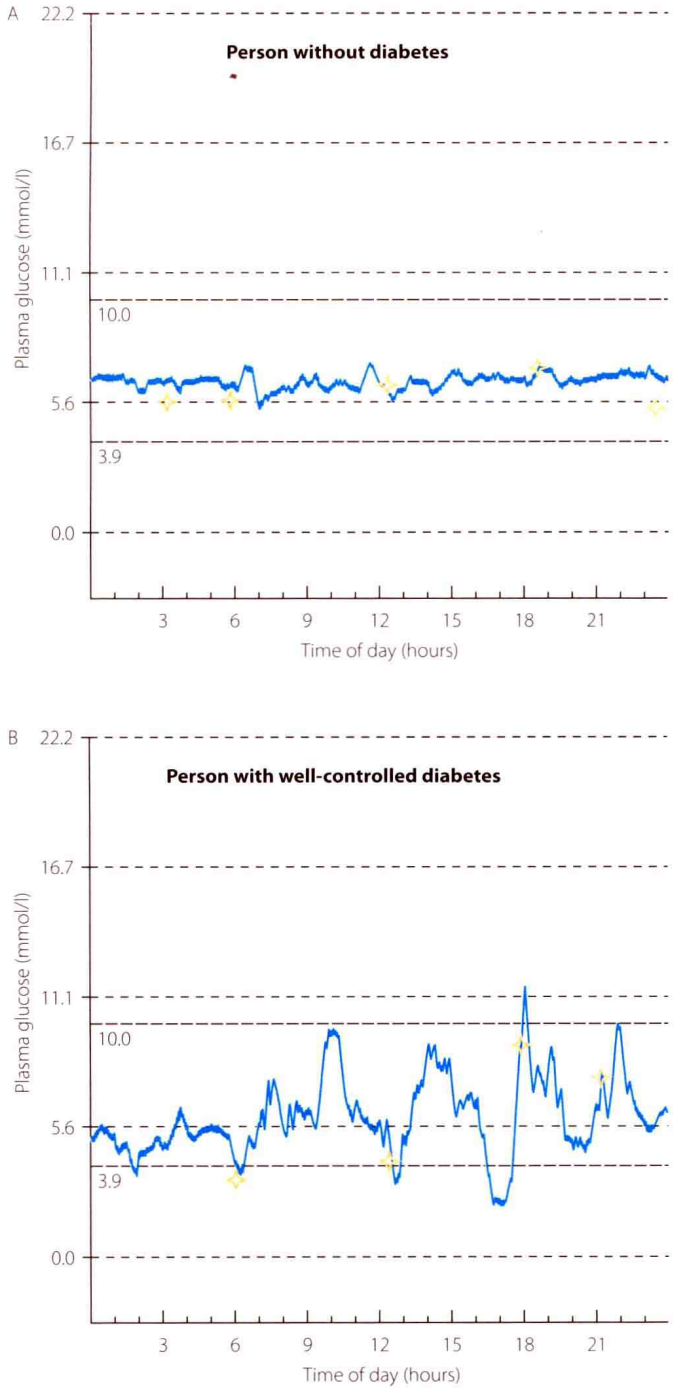

Figure 2 Daily profile from implanted continuous blood glucose monitoring device in (A) person without diabetes; (B) person with well-controlled type 1 diabetes.

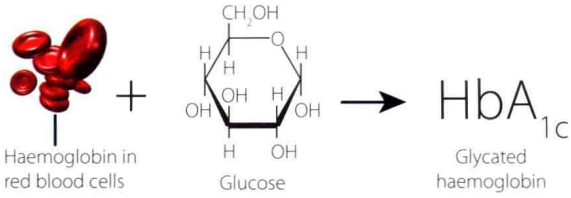

Figure 3 Formation of HbA$_{1c}$.

high. Some anaemias, e.g. haemolytic anaemia and polycythaemia rubra vera can depress HbA$_{1c}$, because the lifespan of the red blood cells is shorter than normal. Abnormal or variant haemoglobins may also affect HbA$_{1c}$ results, as discussed later.

The haemoglobin molecule is composed of four globin protein chains, each with a haem moiety, held together by non-covalent interactions (Figure 4). The 3D structure of the molecule changes when oxygen binds to the haem. In normal adult haemoglobin (HbA), there are 2 α globin chains of 141 amino acids each, coded by DNA on chromosome 16, and 2 β globin chains of 146 amino acids coded on chromosome 11. Fetal haemoglobin, present in babies, binds oxygen with a greater affinity than adult haemoglobin; it contains 2 α chains and 2 γ chains coded on chromosome 11. The γ chain has less positive charges than the adult β chain. Over the first year of life, the production of fetal haemoglobin ceases so that it accounts for less than one per cent of haemoglobin in adults (Figure 5). In certain circumstances due to genetic abnormalities, higher amounts of fetal haemoglobin occur in adults (termed hereditary persistence of fetal haemoglobin) which can lead to problems when using HbA$_{1c}$ to monitor glucose control in diabetes.

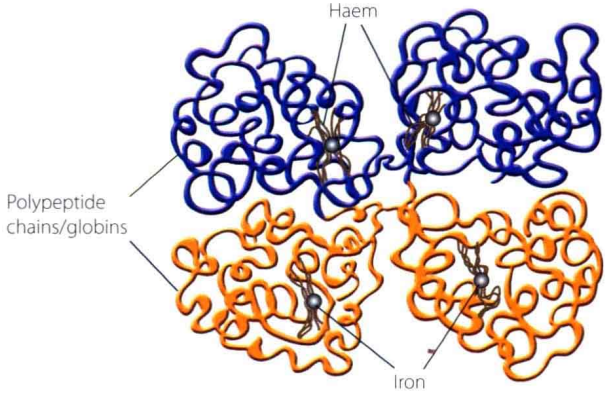

Figure 4 Structure of haemoglobin molecule.