THE RELATIONSHIP BETWEEN PLASMA GLUCOSE IN ORAL GLUCOSE TOLERANCE TEST AND HbA_{1c} IN QUEEN ELIZABETH HOSPITAL KOTA KINABALU

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I dedicated this thesis to my parents.

Siti Khadzirah binti Daud
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ABSTRACT

The blood glucose level measurement is important in the diagnosis of Diabetes mellitus. As recommended by the World Health Organisation (WHO) in 1985, fasting plasma glucose (FPG) level of ≥ 7.8 mmol/L (140 mg/dL) and/or 2-hour post-glucose loading (or random plasma glucose) level of ≥ 11.1 mmol/L (200mg/dL) in Oral Gluose Tolerance Test (OGTT) are used as diagnostic criteria. Both tests are commonly used to diagnose those at risk of Type 2 Diabetes mellitus. However, recently, WHO has recommended that Hemoglobin A_{1c} (HbA_{1c}) with cut-off point of ≥ 6.5% can be used as a diagnostic test for Diabetes mellitus. Hence, this study was undertaken to determine whether the recommendation applies to the patient population in Queen Elizabeth Hospital Kota Kinabalu. The fasting plasma glucose and 2-hour post-glucose loading test were performed using Roche Chemistry Analyzer Modular P800 while for the HbA_{1c} test was estimated using the PDQ Primus Plus HbA_{1c} analyzer at the Department of Pathology, Queen Elizabeth Hospital. The data were analyzed and interpreted using the Statistical Package for The Social Sciences (SPSS) Version 18.0. There was a strong correlation between FPG test and HbA_{1c} test. Similarly, there was a strong correlation between 2-hour post-glucose loading test and HbA_{1c} . In conclusion, there is a strong correlation between FPG, 2-hour post-glucose loading in Oral Glucose Tolerance Test (OGTT) and $HbA_{1c.}$ Hence, HbA_{1c} can be used as the diagnostic criteria with the cut-off point of 6.7% in Queen Elizabeth Hospital, Kota Kinabalu.

ABSTRAK

HUBUNGAN DIANTARA TAHAP GLUCOSA PLASMA DARAH DALAM UJIAN TOLERANSI GLUKOSA DARAH DAN HbA_{1C} DI HOSPITAL QUEEN ELIZABETH, KOTA KINABALU.

Pengukuran paras glukosa dalam darah adalah penting untuk mendiagnosis penyakit kencing manis. Kriteria pendiagnosan kencing manis yang disyorkan oleh Pertubuhan Kesihatan Sedunia (WHO) adalah berdasarkan ujian glukosa plasma ketika berpuasa dengan paras glukosa ≥ 7.8 mmol/L (140 mg/dL) dan/atau ujian glukosa plasma 2-jam selepas pengambilan glukosa dalam ujian toleransi glukosa dengan paras glukosa ≥ 11.1 mmol/L (200 mg/dL). Kedua-dua ujian tersebut digunakan secara berleluasa sehingga ke hari ini sebagai ujian diagnosis penyakit kencing manis. Walaubagaimanapun, baru-baru ini Pertubuhan Kesihatan Sedunia (WHO) mengesyorkan bahawa ujian Hemoglobin A_{1c} (HbA_{1c}) dengan paras ≥ 6.5% juga boleh digunakan sebagai ujian diagnosis penyakit kencing manis. Oleh yang demikian, kajian ini dijalankan adalah untuk menentukan samada syor terbaru Pertubuhan Kesihatan Sedunia (WHO) menggunakan ujian HbA_{1c} sebagai ujian diagnosa Diabetes mellitus sesuai digunakan ke atas populasi pesakit di Hospital Queen Elizabeth, Kota Kinabalu. Ujian-ujian glukosa plasma berpuasa dan 2-jam selepas pengambilan glukosa dalam ujian toleransi glukosa dijalankan menggunakan mesin analisis kimia Modular P800 Roche manakala ujian HbA_{1c} dijalankan menggunakan mesin PDQ Primus Plus Boronate Affinity Method di Jabatan Patologi Hospital Queen Elizabeth. Data-data keputusan dianalisis dan diinterpretasi menggunakan program Statistical Package for The Social Sciences (SPSS) Versi 18.0. Terdapat hubungan korelasi yang kuat di antara ujian glukosa plasma berpuasa dan ujian HbA_{1c} dan korelasi di antara ujian glukosa plasma 2-jam selepas pengambilan glukosa dan HbA_{1c} juga memberikan hubungan korelasi yang hampir serupa. Secara kesimpulannya, wujudnya hubungan korelasi yang kuat di antara ujian glukosa berpuasa dan 2-jam selepas pengambilan glukosa dalam ujian toleransi glukosa dan HbA_{1c} dan ujian HbA_{1c} dengan paras 6.7% boleh digunakan sebagai ujian diagnosa kencing manis di Hospital Queen Elizabeth, Kota Kinabalu.

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AUC	Area Under Curve
CAP	College of American Pathologist
CDC	Center for Disease Control
CI	Confidence Interval
CPNU	Subcommittee on Nomenclature, Properties and Units
CSF	Cerebrospinal Fluid
DCCT	Diabetes Control and Complications Trial
EDTA	Ethylenediaminetetraacetic acid
FPG	Fasting Plasma Glucose
HbA_{1c}	Hemoglobin A_{1c}
HK	Hexokinase
HPLC	High Performance Liquid Chromatography
IFCC	International Federation of Clinical Chemist
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IUPAC	International Union of Pure and Applied Chemistry
MODY	Maturity Onset Diabetes of The Young
NaF	Sodium Fluoride
NADP	Adenosinedinucleotide Phosphate
NGSP	National glycohemoglobin Standardization Program
NHMS II	National Health and Morbidity Survey II
NHMS III	National Health and Morbidity Survey III
OGTT	Oral Glucose Tolerance Test
Pre-A_{1c}	Labile fraction/ fast Hemoglobin
2HPP	2 Hour Postprandial
ROC	Receiver Operating Curve
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

LIST OF UNITS

^{0}C	Degree Celcius
mmol/L	millimol per Liter
mmol/mol	millimol per mol
mg/dL	milligram per desilitre
%	Percentage

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Diabetes mellitus is a major worldwide public health problem causing significant mortality and morbidity due to specific diabetes related microvascular complications and increased risk of macrovascular complications such as ischemic heart disease, stroke and peripheral vascular disease (American Diabetes Association, 2011). It is a global epidemic and the most common non-communicable disease that affects more than 150 million people worldwide (Hasni Ibrahim, Adibah Hanim, Shaiful Bahari Ismail, Wan Mohamed Wan Bebakar, 2010). According to the World Health Organisation(WHO) Report on Noncommunicable Diseases (NCD) Country Profile 2014, the noncommunicable diseases are estimated to account for 73% of 146,000 total death in Malaysia, in which 3% of them come from Diabetes mellitus. To date, there are 171 million people worldwide affected with Diabetes mellitus and this is projected to increase to 350 million by 2030 (Chandrasekhar M Sultanpur, Deepa K, S Vijay Kumar, 2010).

The incidence and prevalence of Diabetes mellitus is escalating in the developing and newly industrialized nations (Hasni Ibrahim *et al.*, 2010). In Malaysia, the first National Health and Morbidity Survey (NHMS 1) which was conducted in 1986 had reported that the prevalence of Diabetes mellitus was at a rate of 6.3% (MR Isa, H Zanariah, I Fatimah, Y Ahmad Fardzi, GR Letchuman, WM Wn Nazaimon, WB Wan Mohamed, LR Chandran, GH Tee, H Jamaiyah, 2010). The second National Health and Morbidity II (NHMS II) in 1996 and the National Health and Morbidity III (NHMS III) in 2006 had recorded substantial rise to 8.3% and 14.9% respectively (An Audit of Diabetes and Management, 2008) . According to the World Health Organisation (WHO) estimation that by 2030, Malaysia will have a total of 2.4 million diabetes (at a prevalence rate of 10.8%), compared to 0.94 million in 2000 (an increased of 164%) (An Audit of Diabetes and Management,

2008). In other words, Diabetes mellitus is in a chronic stage which can contribute towards illness, disability and death of persons in Malaysia (An Audit of Diabetes and Management, 2008). However, this condition can be improved with a tight control of blood glucose levels. Diabetes Control and Complication Trial (DCCT) (Goldstein, Little, Weidmeyer, England, Rohfling, Wilke, 1994; Little, Rohlfing, Weidmeyer, Myers, Sacks, Goldstein, 2001; Abbreviated Report of a WHO Consultation, 2011 has recommended serial measurement of whole blood hemoglobin A_{1c} (HbA_{1c}) for diabetes control and management and it was introduced into clinical use in the 1980's (Goldstein *et al.*, 1994).

Based on aetiologies, World Health Organisation (WHO) and the American Diabetes Organisation (ADA) had recommended new classifications of diabetes (Davidson, Shriger, Peters, Lorber, 1999) which are described as follows:

1. Type 1 Diabetes mellitus- also known as insulin-dependent Diabetes mellitus as shown in Figure 1.2. It is caused by the autoimmune destruction of the β-cells of the pancreas and usually leading to absolute insulin deficiency (or insulinopenia) whereby has dependence on the insulin to sustain life and to prevent ketosis. Symptoms normally present such as acute polyuria, polydipsia and rapid weight loss- as shown in Figure 1.1. This subclass of diabetes contributes approximately 5 – 10% of all individuals with diabetes (Provan, 2002; Davidson *et al.*, 1999).
2. Type 2 Diabetes mellitus (refer to Figure 1.3) – Formerly known as maturity-onset or non-insulin-dependent (NIDDM) Diabetes mellitus, results from a combination of inadequate production of insulin and insulin resistance. This type of diabetes contributes 90% of all cases of diabetes. Patients show minimal symptoms and are not dependent on insulin to prevent ketosis (Provan, 2002; Davidson *et al.*, 1999).
3. Gestational Diabetes mellitus – This type of diabetes occurs during pregnancy only and normally resolves post-partum. However, sometimes it can also become an early manifestation of type 2 Diabetes mellitus (Provan, 2002; Davidson *et al.*, 1999). The gestational Diabetes mellitus pathway is shown in Figure 1.4.

4. Maturity Onset of the Young (MODY) diabetes – Nonketotic form of diabetes with very strong genetic determination. MODY sub-type is described in Table 1.1. Several single gene defects with autosomal dominance pattern of inheritance have been identified including the glucokinase gene and several members of the hepatic nuclear factor (HNF) family proteins. Mitochondrial DNA mutations have also been demonstrated to produce diabetes, but are associated with maternal transmission (Provan, 2002; Davidson *et al.*, 1999). The causation of this type of diabetes is shown in Figure 1.5.
5. Secondary to pancreatitis – Recurrent pancreatitis, cystic fibrosis, carcinoma, hemochromatosis). Pheochromocytoma, acromegaly, Cushing's disease or syndrome, glucagonoma, somatostatinoma, thyrotoxicosis, medications (eg. glucocorticoids, oral contraceptives, thiazides) (Provan, 2002; Davidson *et al.*, 1999).

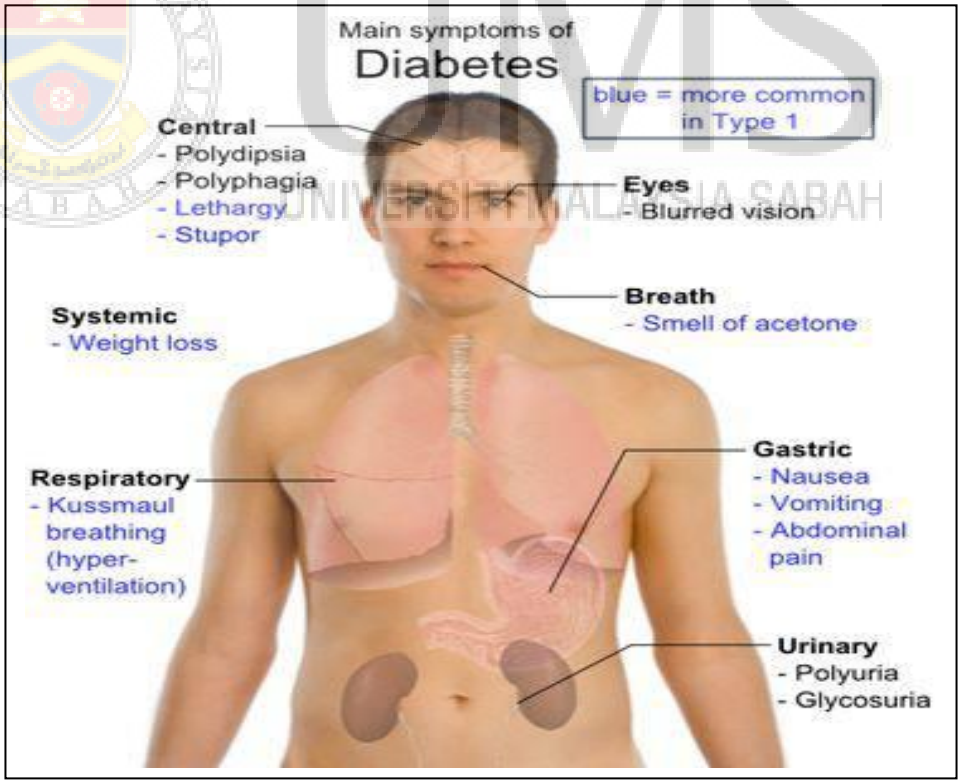

Figure 1.1: Main symptoms of Diabetes mellitus.
Source : http://www.askdrmakkar.com

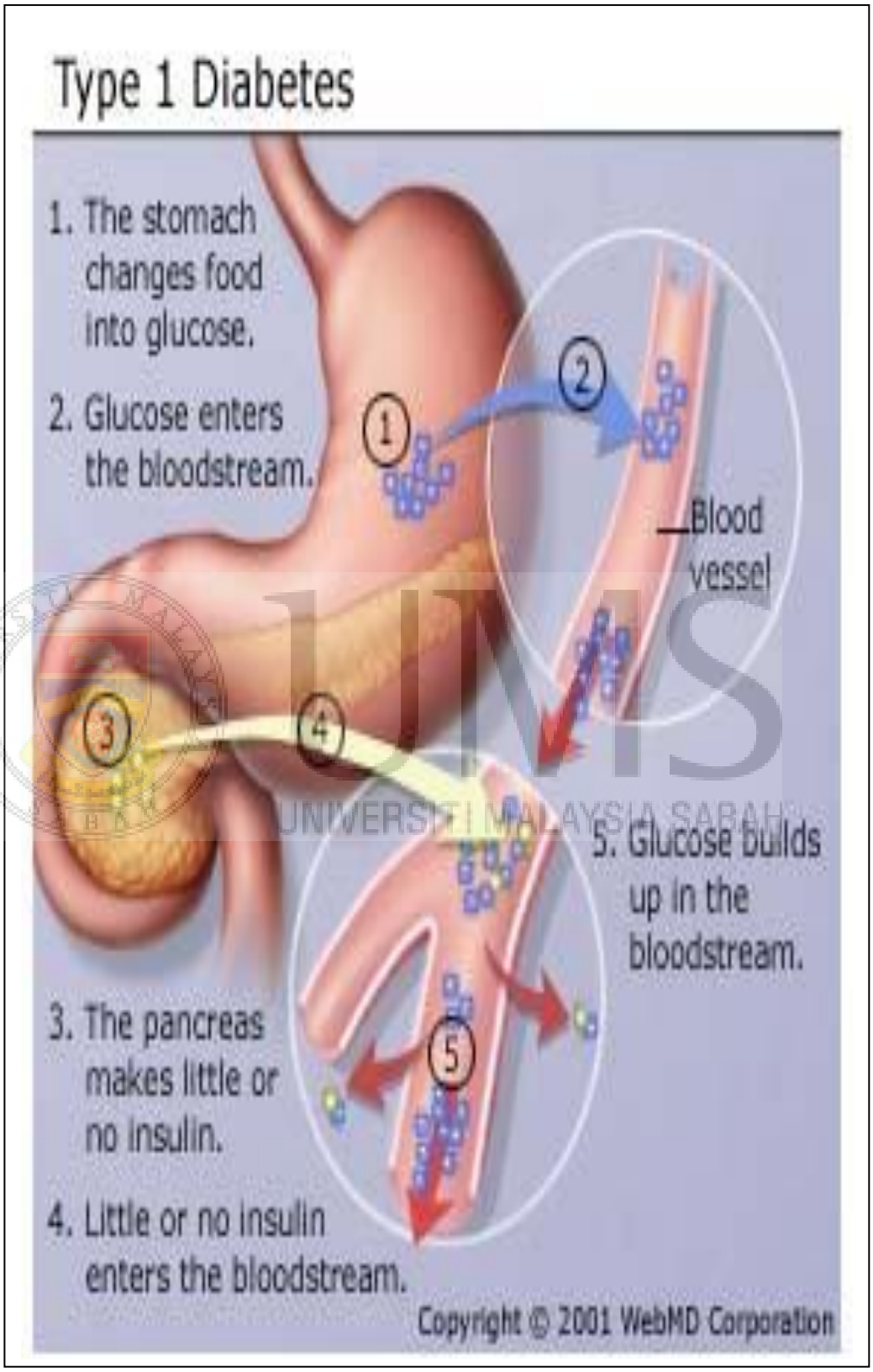

Figure 1.2: Type 1 Causation of Diabetes mellitus.
Source : http://www.trialx.com

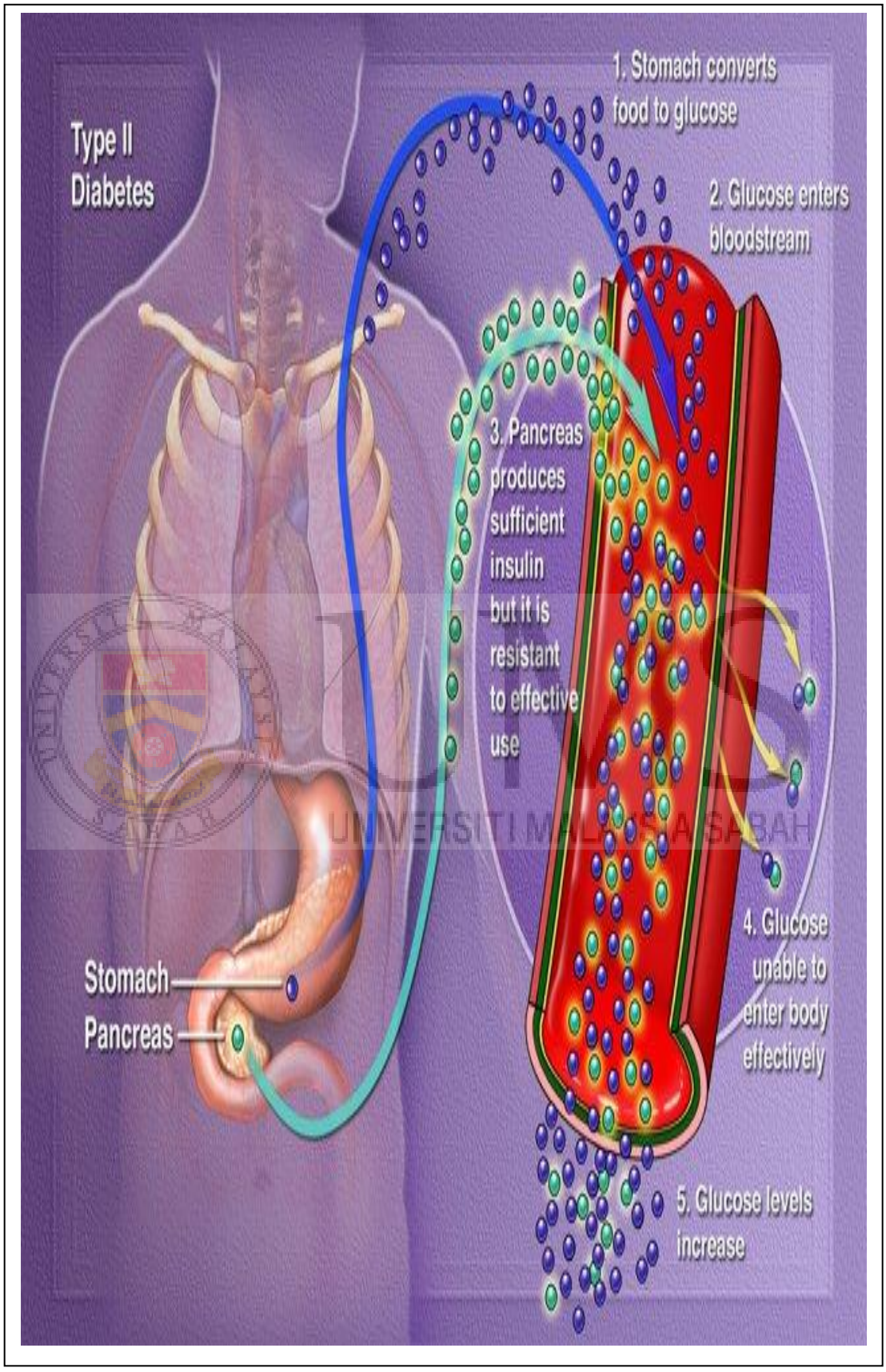

Figure 1.3: Cause of Type 2 Diabetes mellitus.
Source : http://www.odlarmed.com

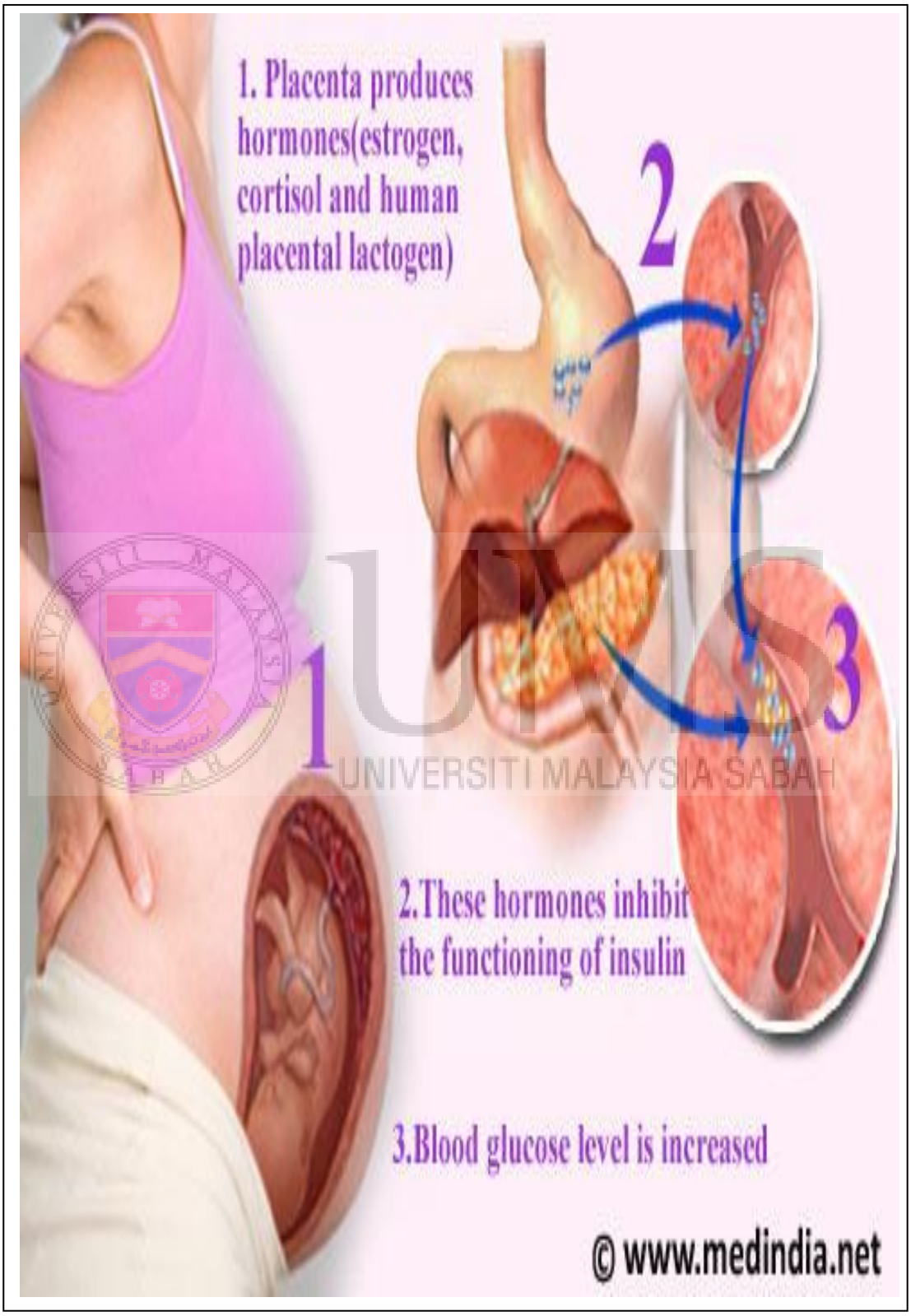

Figure 1.4: Gestational Diabetes mellitus Pathway.
Source : http://www.medindia.net

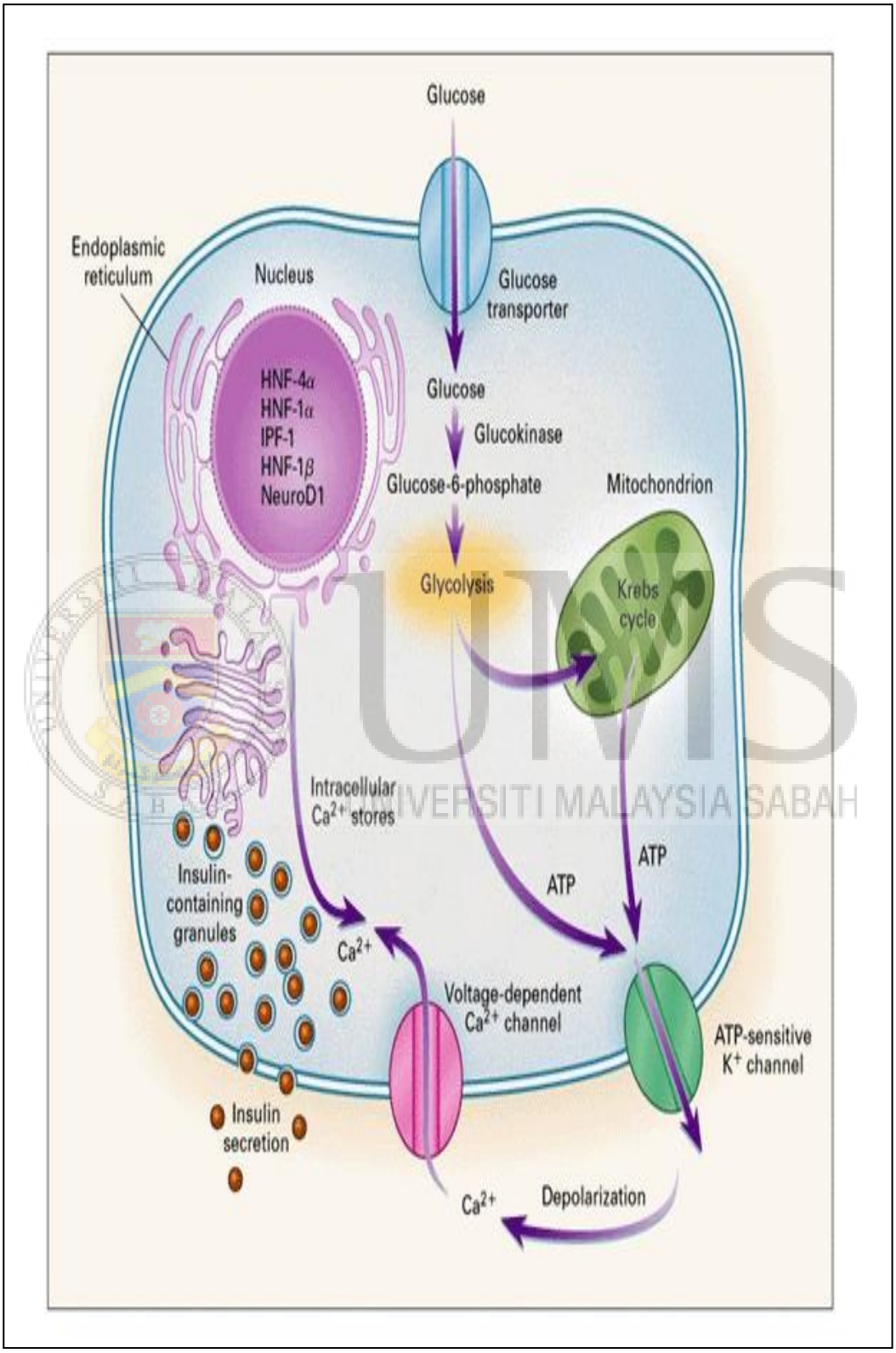

Figure 1.5: Maturity Onset Diabetes of The Young (MODY).
Source : http://www.meddic.jp