Study of the Levels of Serum Copeptin in Patients with Diabetic Retinopathy

Thesis
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Contents

List of Abbreviations

Abbreviation	Full form
2hr PP	2 hour post prandial blood sugar
ACR	Albumin creatinine ratio
ACTH	Adrenocorticotrophic hormone
ADED	Advanced diabetic eye disease
ADPKD	Autosomal dominanat polycystic kidney disease
AGE	Advanced glycation end products
ALE	Advanced lipoxidation end products
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
AVP	Arginine vasopressin
CD55	Cluster of differentiation
CD59	Cluster of differentiation
CT-ProAVP	C-terminal part of the AVP precursor
DAF	Decay accelerating factor
DCCT	Diabetes control and complications study
DESIR	Data From an Epidemiological Study on the Insulin Resistance Syndrome
DIRECT	Diabetic Retinopathy Candesartan Trials
DM	Diabetes mellitus

DME	Diabetic macular edema
DR	Diabetic retinopathy
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme linked immunosorbent assay
ESRD	End stage renal disease
ETDRS	Early Treatment Diabetic Retinopathy Study
FBS	Fasting blood sugar
FBS	Fasting blood sugar
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
HRP	Horseradish peroxidase
IDDM	Insulin dependent diabetes mellitus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LDL	Low density lipoprotein
NGSP	National Glycohemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey
NIDDM	Non insulin dependent diabetes mellitus
NPDR	Non proliferative diabetic retinopathy

OD	Optical density
OGTT	Oral glucose tolerance test
PDR	Proliferative diabetic retinopathy
PKC	Protein kinase C
RAAS	Renin angiotensin aldosterone system
RAGE	Receptor for advanced glycation endproducts
RASS	Renin angiotensin study system
SD	Standard deviation
SPSS	Statistical package for social sciences
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TMB	Tetramethylbenzidine
UKPDS	United kingdom prospective diabetes study
VEGF	Vascular endothelial growth factor
VTDR	Vision threatening diabetic retinopathy
WHO	World health organization

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Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with damage, dysfunction and failure of different organs. **[Genuth et al, 2003]**

Diabetic retinopathy is the leading cause of blindness in patients aged 20 to 74 years. Chronic hyperglycemia affects the retinal vessels resulting in diabetic retinopathy. The risk of development and progression of diabetic retinopathy is closely associated with the type and duration of diabetes. **[Tarr et al, 2012]**

Copeptin is the C-terminal part of the vasopressin prohormone**.** It is relatively stable in the serum and its levels can be measured accurately. It is equimolar to vasopressin in secretion and hence directly reflects its serum levels. It could be used as an early and adequate marker for organ damage. **[Seligman et al, 2008]**

A study done in Denmark revealed a positive correlation between serum copeptin levels and renal impairment and peripheral arterial disease in type 2 diabetic patients. **[Riphagen et al, 2013]**

Aim of the work:

To study the level of copeptin in patients with diabetic retinopathy.

Review of:
Diabetes Mellitus

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. **[Njolstad et al, 2003]**

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014. **[Balakumar et al, 2016]**

There are two main types of diabetes mellitus. Type 1 diabetes is insulin dependent diabetes mellitus (IDDM), and is caused by lack of insulin secretion by beta cells of the pancreas. Type 2 diabetes, also called non-insulin dependent diabetes mellitus (NIDDM), is caused by decreased sensitivity of target tissues to insulin which is later followed by decreased secretion of insulin. **[Maahs et al, 2010]**

Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide. The incidence of T1D is increasing with age in most populations with the highest incidence observed in the 10–14 year olds. **[Maahs et al, 2010].**

Type 1 diabetes is the result of an autoimmune reaction to the islets cells of the pancreas **[Holt, 2004]**.

Type 1 diabetes occurs as a consequence of the organ-specific immune destruction of the insulin-producing β-cells in the islets of Langerhans within the pancreas. It develops as a consequence of a combination of genetic predisposition and largely unknown environmental factors. [**Bluestone et al, 2010**]

Pathogenesis of type 2 diabetes

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin and insulin secretion. In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance **[Holt, 2004].**

Other types of diabetes include Gestational diabetes mellitus (GDM), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Individuals with IFG or IGT have been referred to as having prediabetes, indicating the relatively high risk for the future development of diabetes. IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes as well as cardiovascular disease. **[Genuth et al, 2003]**

Diagnosis of Diabetes Mellitus

Clinical presentation:

Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the non ketotic hyperosmolar syndrome. **[Genuth et al, 2003]**

Biochemical diagnosis:

National Health and Nutrition Examination Survey (NHANES) data indicate that an A1C cut point of ≥6.5% should be diagnostic of diabetes. The A1C test should be performed using a method that is certified by the NGSP and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. In addition to the A1C test, the FPG and 2-h PG may also be used to diagnose diabetes **(Table A)**. The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose-based test. A fasting glucose cut point of ≥126 mg/dL (7.0 mmol/L) is diagnostic of diabetes. Two hour post prandial (2hr PP) ≥200 mg/dL (11.1 mmol/L) or random blood glucose (RBG) ≥200 mg/dL (11.1 mmol/L) should also diagnose diabetes. This is represented in table A. **[ADA, 2017]**

Table A: Criteria of diagnosis of diabetes mellitus [ADA, 2017]

A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

During the earlier stages of diabetes the patients may remain asymptomatic for long periods. The early diagnosis and management of diabetes may delay the incidence of diabetic complications and decrease the occurrence of acute complications. Hence the American Diabetes Association recommends screening for type 2 diabetes annually in patients 45 years and older, or in patients younger than 45 years with major risk factors. These include:

- HbA1c> 5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing,
- Acanthosis nigricans,
- Cardiovascular disease,
- First-degree relative with type 2 diabetes,
- HDL cholesterol level < 35 mg per dL and/or a triglyceride level > 250 mg per dL,
- High-risk ethnicity: black, Native American/Alaska

Native, Hispanic/Latino, Asian American, and Native Hawaiian/Pacific Islander,

- Hypertension (blood pressure > 140/90 mm Hg or taking medication for hypertension) ,
- Physical inactivity,
- Polycystic ovary syndrome
- Women who had gestational diabetes or who delivered a baby weighing > 9 lb.

[ADA, 2015]

Prolonged hyperglycemia, especially if uncontrolled leads to a collection of organ dysfunction. Diabetes commonly causes diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.