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TYPE 2 DIABETES MELLITUS: CLINICAL AND AETIOLOGIC TYPES, THERAPY AND QUALITY OF GLYCAEMIC CONTROL OF AMBULATORY PATIENTS
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TYPE 2 DIABETES MELLITUS: CLINICAL AND AETIOLOGIC TYPES, THERAPY AND QUALITY OF GLYCAEMIC CONTROL OF AMBULATORY PATIENTS

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ABSTRACT

Background: **Type 2 diabetes is a heterogeneous disease with multiple causes revolving around beta cell dysfunction, insulin resistance and enhanced hepatic glucose output. Clinical judgement based on obesity status, age of onset and the clinical perception of residual beta cell insulin secretory function (hence insulin-requiring or not), has been used to determine therapeutic choices for each patient. Further laboratory testing of the clinically defined type 2 diabetes unmasks the various aetiologic types within the single clinical group.**

Objective: **To determine the aetiological types of the clinically defined type 2 diabetic patients, their chosen therapies at recruitment and the quality of glycaemic control achieved.**

Design: **Descriptive cross-sectional study.**

Setting: **Diabetes out-patient clinic of Kenyatta National Hospital, Nairobi, Kenya.**

Results: **A total of 124 patients with clinical type 2 diabetes were included, 49.2% were males. The mean duration of diabetes in males was 26.09 (20.95) months and that of females was 28.68 (20.54) months. The aetiological grouping revealed the following proportions: Type 1A-3.2%, Type 1B-12.1%, LADA-5.7%, and "true" type 2 diabetes 79.0%. All the patients with Type 1A were apparently, and rightly so, on "insulin-only" treatment even though they did not achieve optimal glycaemic control with HbA_1c % = 9.06. However the study patients who were type 1B and LADA were distributed all over the treatment groups where most of them did not achieve optimal glycaemic control, range of HbA_1c of 8.46 -10.6%. The patients with "true" type 2 were also distributed all over the treatment groups where only subjects on 'diet only' treatment had good HbA_1c of 6.72% but those in other treatment groups did not achieve optimal glycaemic control of HbA_1c, 8.07 - 9.32%.**

Conclusion: **Type 2 diabetes is a heterogeneous disease where clinical judgement alone does not adequately tell the various aetiological types apart without additional laboratory testing of C-peptide levels and GAD antibody status. This may partly explain the inappropriate treatment choices for the various aetiological types with consequent sub-optimal glycaemic control of those patients.**

INTRODUCTION

The National Diabetes Data Group (1979) classification (1) subdivided diabetes according to perceived need for insulin therapy. The WHO (1997) classification (2) sought to replace the previous categories with a functional measure based on insulin deficiency.

Type 2 diabetes is a heterogeneous disease with multiple causes revolving around beta cell

dysfunction and insulin resistance, the latter process is largely determined by obesity (3,4). However the cut-off level of obesity and the proportions thereof vary in populations. C-peptide is considered a good marker of insulin secretion because of its equimolar secretion with insulin, negligible hepatic extraction (5-7) and constant peripheral clearance at different plasma concentrations and in the presence of alterations in plasma glucose concentrations (7,8). Fasting C-peptide alone is easy to obtain and correlates well with stimulated C-peptide.

Therapy for glycaemic control has been largely guided by the perceived class of insulin requiring or non-insulin requiring types, this classification being informed by clinical judgement based on age of onset and obesity status. It is unclear whether the defects in insulin- sensitivity and insulin secretion occur in parallel and progress at the same velocity through the time course of the disease once the diagnosis has been made (9-12) and particularly when the diabetes is being treated by mono or multiple drug strategies. Suffice to say that glycaemic control of diabetes has remained largely an elusive goal in many regions of the world even where resources are considered to be relatively abundant. Hattersley (13), opines that treatment decisions in diabetes should depend on genetic aetiology of diabetes and not just on age of onset, Body Mass Index (BMI) and severity of hyperglycaemia. He admits that high costs remain a deterrent to detailed testing in diabetes care. This study first classified patients with type 2 diabetes on clinical grounds, then re-categorised them using laboratory tests and evaluated the therapeutic choices they were using that had been initiated based on clinical judgement.

MATERIALS AND METHODS

Subjects: Patients with clinically defined type 2 diabetes were recruited and included in the study. Type 2 diabetes was defined as diabetes mellitus of onset at age 40 years and above or if less than 40 years the person had been on oral glucose lowering agents for at least six months. Furthermore, the patients who were classified as obese by body mass index (BMI); (BMI > 25kg m^2) were systematically sampled where every other patient fitting the inclusion criteria was enrolled on each clinic day. This clinic conducts only one major diabetes clinic each week. The non-obese (BMI $\leq$25kg/m^2) patients were recruited consecutively because they are relatively fewer in this clinic. Each recruited study participant was re-evaluated for weight and height in the standard way to ascertain the BMI. A detailed history of diabetes including date of onset, family history, the contemporary and past treatment modality or profile were obtained and recorded. Family history of diabetes was recorded as present or absent; treatment choices as; diet-only, oral glucose lowering agents-only, insulin only and combined insulin and oral agents. There were multiple generics of the oral agents (both sulphonylureas and metformin) in use by the study patients either as single or combination oral agents therefore no further attempts were made to define them in details beyond their categories as oral glucose lowering agents. The information was captured as the number (proportion) of study patients on each treatment modality / choice. Laboratory work-up of fasting C-peptide levels, GAD antibody status, glycated haemoglobin (HbAIc) and fasting glucose were done. A sample of 8mls of venous blood was withdrawn from antecubital vein. C-peptide was determined by Elisa (human bioassay technique, *US biological,* a solid two-site enzyme immunoassay with a lowest detection limit of 0.3 ng/ml and precision CV<10%. GAD antibody status was also determined by Elisa technique (*diaplets anti-GAD plus, Roche Applied Science Division* for Quantitative Determination of Antibodies to GAD-65). Data on C-peptide and GAD antibody status were used to re-categorise patients as type lA autoimmune, type IB-idiopathic, latent autoimmune diabetes of adults (LADA) and "true' type 2 diabetes. Upon re-categorisation the study participants were evaluated for clinical characteristics, current therapeutic choices in use and respective levels of glycaemic control achieved. The data were summarised in categories where appropriate and continuous variables were summarised in means and standard deviation and proportions. Differences in means between males and females and various treatment modalities were tested by students t-test where indicated. The level of statistical significance was taken at $p<0.05$.

RESULTS

A total of 124 subjects were included in the study. Their clinical and laboratory characteristics are summarised in Table 1.

Table 1
Characteristics of the study subjects by gender

	Male (n=61)	Female (n=63)	P-value
Age (years) Means ± SD	M-49.08	M-45.90	P<0.05*
	SD-10.81	SD-12.44	
Duration of diabetes means	M-26.09	M-28.68	P>0.05,NS
(SD) months	SD-20.95	SD-20.54	
BMI (Kg/m^2)	M-24.99	M-27.01	P<0.01*
	SD-5.44	SD-5.01	
FBG mmo/1	M-9.11	M-9.15	P>0.05
	SD-2.00	SD-4.79	
HbA_1c%	M-8.30	M-8.90	P<0.05*
	SD-2.00	SD-1.87	
C-peptide(ng/ml)	M-5.09	M-5.06	P>0.05
	SD-4.46	SD-4.09	
Treatment choices			
proportion of patients			
Diet-only	6.7%	9.5%	P>0.05
OHA-only	48.3%	44.4%	P>0.05
Insulin-only	35.0%	31.7%	P>0.05
OHA+Insulin	10.0%	14.4%	P>0.05

* = Statistically significant differences between males and females
FBG = Fasting blood glucose
OHA = Oral hypoglycaemic agents
NS = Not significant
SD = Standard deviation
M = Mean

Table 2
Characteristics of the study population by their aetiologic types

	Type 1A	Type 1B	LADA	"True" Type 2
No. %				
Male (M)	M-(1) 1.6%	M-(7) 11.5%	M-(5)8.2%	M-(48) 78.7%
Female (F)	F-(3) 4.8%	F-(8)12.7%	F-(2) 3.2%	F-(50) 79.3%
Mean age(years)	M-50.67	M-46.33	M-49.00	M-49.33
	F-29.00	F-36.88	F-52.00	F-47.35
Mean BMI (Kg/m^2)	M-21.07	M-18.07	M-23.20	M-26.27
	F-22.35	F-21.66	F-25.17	F-27.97
Mean C-peptide	M-0.11	M-0.03	M-2.33	M-6.28
(ng/ml)	F-0.00	F-0.10	F-1.320	F-6.08
Mean duration of diabetes	M-23.00	M-25.33	M-7.50	M-28.38
(Months)	F-60.00	F-38.63	F-36.50	F-25.59
Mean fasting blood	M-13.17	M-8.88	M-8.72	M.7.65
glucose (mmol/l)	F-3.00	F-7.49	F-10.30	F-8.37

M = Male F = Female

Table 3

Aetiologic types, therapy at enrolment and mean glycated haemoglobin of the study subjects

Mean HbAlc/ Treatment choice	Type 1A (n=4)	Type 1B(*) (n=15)	LADA(*) (n=8)	Type 2 (μ) (n=98)
OHA-only				
No. (%)	0 (0.00%)	1 (6.7%)	4 (57.1%)	50 (51.0%)
HbA_Ic %	-	6.72	9.330	8.07
OHA + insulin				
No. (%)	0 (0.00%)	2 (13.3%)	1 (14.3%)	15 (15.3%)
HbA_Ic %	-	8.46	8.49	9.32
Insulin- only				
No. (%)	4 (100.0%)©	11 (73.3%)	1 (14.3%)	25 (25.5%)
HbA_Ic %	9.06	10.67	10.930	8.62
Diet - only				
No. (%)	0 (0.00%)	1 (6.7%)	1 (14.3%)	8 (8.2%)
HbA_Ic %	0	8.80	8.19	6.92

OHA = Oral Hypoglycaemic Agents

© = Virtually all patients categorised as type IA were on treatment with insulin only, however they were not reaching glycaemic targets.

* = Other types (lB and LADA) of diabetes were on various therapies but did not achieve optimal glycaemic control.

μ = "True" Type 2 diabetes were also receiving multiple therapies without reaching desired targets except those on "diet - only" therapy.

DISCUSSION

At recruitment of subjects into this study, the defining characteristics were clinically defined type 2 diabetes with a body mass index of either $\leq 25\ Kg/m^2$ or above $25\ Kg/m^2$. Other clinical and laboratory parameters were subsequently determined which unmasked a previously unknown heterogeneity within those patients who were clinically defined as type 2 diabetics.

Evidence from UKPDS (14) suggested that patients with type 2 diabetes and obesity (BMI >25 Kg/m^2) should be treated with metformin as first line and the non-obese (BM1$\leq$ $25Kg/m^2$) should be given either sulphonylurea alone and / or combination with metformin. The message implied is that BMI does guide therapeutic choices.

Probably BMI of our study patients was used to inform the primary clinicians of the perceived appropriate choices of treatment. Some studies have looked at what factors including BMI (as a measure of obesity) may predict response to treatment with sulphonylureas or metformin and they suggested that BMI does not seem to influence treatment response with either class of drugs (15-17) even though BMI is used to inform treatment choices. Whatever factors that are considered in making choices of therapy adequate glycaemic control is the main goal of therapy in diabetes both in type 1 (18) and type 2 (19) because it is beneficial.

The significance of this study is that all study participants were clinically defined to have type 2 diabetes and followed up as such. Hence their therapeutic choices were essentially those designed for such patients. It is therefore no wonder that the subjects who were later found to fit the category of type 1 B diabetes were on oral agents with or without insulin. The oral glucose lowering agents included metformin and sulphonylureas (either glibenclamide or chlorpropamide) in various dosages.

On re-categorising the patients by laboratory testing (C-peptide levels and GAD antibody status) the patients fell into the various types of diabetics shown including type lA (autoimmune) and IB (idiopathic), latent autoimmune diabetes of adults (LADA) and 'true' type 2 diabetes.

The glycaemic control remained sub-optimal in all those patients who remained 'true' type 2, LADA and even those who were coincidentally type 1 and supposedly on rightful insulin- therapy at the time of enrolment (Table 3). Indeed only 'true' type 2 diabetic patients on diet-only therapy had good glycaemic control. The better glycaemic control in the diet-only treatment group has been observed before in this clinic although we did not do C-peptides in that study (20). A significant contribution from their adequate endogenous beta cell function, read high C-peptide levels, explains the superior control (Table 2).

Achieving glycaemic targets in type 2 diabetes remains a major challenge during their clinical care. Cook *et al* (21) demonstrated that delayed or insufficient intensification of pharmacological management is a cause of failure to attain glycaemic goals in their urban African-American- population. Our study has revealed the limitation of clinical judgement for telling the type of diabetes with certainty so that therapy can be optimised. However clinical judgement has not been condemned wholesome by this study. Rather it seems to suggest the need for early insulin therapy in the lean (BMI≤ 25 Kg/m^2) type 2 diabetic patients in this population who are likely to be the more heterogeneous group with higher proportion of aetiologic type 1 diabetes. Classification of diabetes is still evolving and so far inconclusive. Consequently, therapeutic approaches to types of diabetes as currently classified (by clinical judgement) provide a lot of room for debate and use of various treatment choices, maybe inappropriately, although that is what is universally available to clinicians in routine clinical practice.

Our study did cross-sectional fasting C-peptide assay where the extent of sulphonylurea stimulation effect in patients using them could not be under-estimated even though the glycaemic control was sub-optimal. Either the beta-cell stimulation was sub-optimal with contemporary doses that were in use or the peripheral insulin resistance was the determining factor that was not addressed in therapy. Alternatively, both beta cell stimulation and peripheral insulin resistance were inadequately addressed, especially amongst patients re-categorised as "true" type 2 diabetes whose duration of diabetes was five years or less when they were expected to retain some insulin secretory capability. The contribution of peripheral insulin resistance was implied by the relatively high levels of C-peptide in a significant proportion of our patients with "true" type 2 diabetes and comparatively higher BMI than the other aetiologic types. We did recognise that poor glycaemic control may not wholly be attributable to beta cell and/or insulin resistance factors but the mind of the patients may also be involved .The patients' attitudes and perceptions and their participation in self-care are particularly important in improving therapeutic goals of glycaemia (22), although they were not evaluated in the subjects in this study.

Type 2 diabetes is a progressive disease (11) in spite of therapies that are in use at onset of the disease (23). There are no immediate therapeutic answers to declining beta cell function of type 2 diabetes. ADOPT study (24) was a step towards this direction where preservation of beta cell was an outcome measure. Similarly there is no consensus, so far, on definition (25) and management (26) of LADA. Pozzilli *et al* (26) have suggested that therapy which would influence the speed of progression towards insulin dependency and in the process protect residual C-peptide secretion preferable for latent auto-immune diabetes of adults (LADA).

Insulin availability and accessibility to those who need it, especially in sub-Sahara Africa, is still precarious (27). Even where insulin is already available, there is inertia in initiating patients with type 2 diabetics on it (28). Our study patients had diabetes for five years and less apparently many of them, maybe, needed either basal insulin or just optimisation of the appropriate choice of therapy at the time of the study.

In conclusion, successful glycaemic control in patients with diabetes mellitus will require more understanding of the disease processes in the various classes, the operating clinical-laboratory predictors for the disease class/type and the appropriate and optimal therapeutic choices. Therefore, correctly classifying diabetes at the earliest time of clinical care would facilitate effective advice to the patient and inform the preparation for an individualised treatment programme. This approach will secure maximum participation in self-care of each patient with diabetes. When patients were more satisfied with their physicians' communication skills (29) and participate more in their own treatment (30), they were found to be more adherent to self-care recommendations and achieve better health outcomes. Not all hyperglycaemia is the same, states Fowler (31). The patients living with diabetes and their healthcare providers need to know as much in order to embrace the varied therapeutic options and combinations that may be required often.

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