Review Article

Cardiovascular Risk Assessment in Prediabetes and Undiagnosed Diabetes Mellitus Study: International Collaboration Research Overview

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Abstract

The study aims to develop a screening protocol for the risk of future cardiovascular disease and diabetes mellitus in people with prediabetes and undiagnosed diabetes; and to establish a framework for early identification and intervention of prediabetes including strategies for holistic management and monitoring of progression. The first phase is to identify prediabetes and undiagnosed diabetes in volunteers who are ≥18-years-old for 5 years. Point-of-care testing and questionnaire will be used to screen for prediabetes and cardiovascular disease. We anticipate screening more than 2000 individuals of both genders by the end of first phase. The second and third phases which shall run for 5-10 years will be longitudinal study involving participants identified in the first phase as having prediabetes without dyslipidaemia, or clinically established cardiovascular disease. The second phase shall focus on preventive management of risk of progress to diabetes with explicit diagnosis of cardiovascular disease. Oxidative stress measurements will be performed cum evaluation of the use of antioxidants, exercise, and nutrition. The third phase will include probing the development of diabetes and cardiovascular disease. Binomial logistic regression would be performed to generate and propose a model chart for the assessment of cardiovascular disease risk in prediabetes.

Keywords: Early diagnosis, Early intervention, Holistic health management, Public health screening

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Introduction

Epidemiological information on prediabetes individuals is unknown or not clear. For instance, in the Australian population, epidemiology data have indicated 10% prevalence of prediabetes,[1] while archived pathology data have indicated greater than 33% for prediabetes and 20% previously unknown diabetes (UDM).[2] The ''at risk'' of future cardiovascular disease (CVD) and data on this phase are also not clear. The risk is due to ongoing and unmanaged hyperglycaemia toxicity;[3] and the same applies to undiagnosed diabetes. Although screening programs for ''risk of CVD in diabetes'' exist such as the Framingham flow algorithm and the chart from New Zealand Guidelines Group, diabetes, and smoking status are dichotomous (''YES'' or ''NO'') variables. The problem of being dichotomous is that: Firstly, hyperglycaemia in the prediabetes person is over-looked via a ''NO'' answer, whereas assessment and treatment of CVD risk in prediabetes should be as in diabetes mellitus (DM).[3] Secondly, Smoking is an age-old CVD risk factor, due to its oxidative stress effect. However, smoking factor is captured in the current charts but non-smoking individual who may be suffering hyperglycaemia-induced oxidative stress and/or other forms of chronic stress is not.

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Thus, the risk of future CVD in prediabetes is therefore inadequately assessed and at least two risk factors *viz* hyperglycaemia and the non-smoking individual who may have hyperglycaemia-induced oxidative stress and/or other forms of chronic stress. These are not considered in the current chart, though this synopsis was presented in a hypothesis paper.[4]

Materials and Methods

Current research

A search in PubMed database using ''cardiovascular risk assessment in prediabetes and undiagnosed diabetes,'' as key words, for articles published the last 3 years (after the hypothesis paper) showed that the risk of future CVD in prediabetes is still being inadequately assessed. However, there are reports from the past 3 years that affirm the evidence of the risk of future CVD in prediabetes and the implications of management. For instance, one of the reports indicated that fasting plasma glucose level may help in identifying apparently healthy persons with early metabolic abnormalities who are at increased risk for CVD.[5] Others reported that upto 12% of prediabetes individuals develop DM per year.[6,7] While nutritional care and physical activities are the part of recommended management regimens for people at risk of developing DM,[6] young people with prediabetes have great potential to revert to normal unlike adults.[7] Another affirmative report included that "…identifying prediabetes, even with algorithms, predicts long-term CV events."[8]

Further, a meta-analysis did affirm that holistic interventions including diet, exercise and pharmacotherapy, successfully delayed or prevented progression of prediabetes to DM,[9] while a systemic review affirmed that prediabetes increases the risk for cardiovascular disease.[10] These reports show ever increasing evidence of CVD risk in prediabetes. What is still being omitted is that the risk assessment exists for diabetes, but not prediabetes or undiagnosed diabetes mellitus.

Results

Translational research need

Development of diabetes is complex hence calls for various approaches to its investigation. One approach is metabolomics, which involves investigation of metabolites' patterns and interaction prior to the detection of a gross phenotypic change reflecting disease, [11-13] including diabetes.

Whilst the pathogenesis of diabetic complications is incompletely understood and is likely to involve several inter-dependent cellular processes, it is understood that appropriate glycemic control is crucial to delay or prevent the progression of prediabetes.[12] In this regard, the generation of free radicals is an important consideration, especially considering smoking as a CVD risk factor and the potential role of antioxidants consumed as nutritional supplements to manage oxidative stress.

However, management of stress among non-smokers who are at risk of DM and/or CVD is yet to be a part of clinical practice. In other words, oxidative stress research in diabetes is yet to be translated for clinical practice. Nevertheless, there is scientific underpinning for exercise therapy, nutrition, and social support to manage stress and weight.[14-16] In this context, changes in the metabolites are thought to be useful to predict and/or to prevent subsequent phenotypic changes that are associated with diabetes development. Two translational needs associated with this are medical nutrition therapy,[17,18] and exercise science.[19,20]

Cardiovascular diseases are well-established as leading contributors to the burden of disease.[21,22] An estimated 16.7 million, or 29.2% of global deaths, result from the various forms of CVD, many of which are preventable and are due to the major primary risk factors, *e.g.* unhealthy diet, physical inactivity, and smoking. About 80% of CVD deaths worldwide take place in developing, low- and middle-income countries and these countries also account for 86% of the global CVD burden.[21,23]

Nigeria is currently undergoing rapid epidemiological transition of metabolic disorders,[24] and demographic changes such as ageing, and the undesirable risk factors such as obesity and sedentary life have been implicated as causes.[25-28] A report shows that Nigeria has the highest number of adults with diabetes in sub-Saharan Africa; with 2.8 million adults diabetics in the year 2010 and an estimated 5.3 million by the year 2030 and mean annual increment of 125000.[29] The prevalence of diabetes in Nigeria population and world population in 2010 was 4.7 and 3.9%, respectively; and is projected to rise to 5.5 and 4.3% in both populations, respectively, by the year 2030.[29] It is worthy of note that there is paucity of reports on diabetes and dyslipidaemia in Nigeria; and the majority of the available few reports are based on health institutional surveys in urban areas. What occurs in communities, such as rural villages in Ndokwa local government areas of Delta state, with very little or no health facilities and/or interventions remain a mirage.

In Delta State of Nigeria, only one study was identified and it reported a prevalence of 15.9%, with 11.4%

diagnosed and 45% undiagnosed diabetes in the study population.[30] Worrisomely, a previous study had assessed features of lipid profile among DM in Delta State and found that out of 220 patients:[31] 84.5% had not had a lipid profile test for the past 1 year, 67.3% could not afford the test annually, and only 21.8% were aware of the need for the test.

Surely, these figures are a reason for concern. In America, it is recommended that all adults with diabetes should undergo, at least annually, a fasting lipid profile test, to monitor lipid disorders.[32] In Australia, an audit of archived clinical pathology data indicated that dyslipidaemia is as high as 100 and 74% in DM and prediabetes, respectively.[2]

Discussions

Objectives

The aim of this ''cardiovascular risk assessment in prediabetes and undiagnosed diabetes study'' also to be known as 'prediabetes and cardiovascular complications study (PACCS)' is to develop a screening protocol for the risk of future CVD in prediabetes and undiagnosed diabetes. Further, to establish a criterion for early identification and intervention of prediabetes. To this end, the study focus shall include the following:

Diagnosis and diagnostic monitoring

''Establishment of endpoints and baseline markers with relevance for systemic toxicity testing'' for clinical management of prediabetes and undiagnosed diabetes in humans. To achieve this; the study views 'systemic toxicity' in diabetes pathogenesis as hyperglycemia-induced vasculopathy *vis-à-vis* CVD. Further, the study defines vasculopathy as any of the Virchow's triad *viz*: Atherothrombosis, endothelial dysfunction, and stasis. The study sets to develop a separate screening chart for the risk of future CVD in people with prediabetes and undiagnosed diabetes. Other secondary focus is to validate oxidative stress panel (OSP) as a diagnostic tool for assessment and management of oxidative damage in diabetes pathogenesis; to investigate alternative testing strategies for appropriate monitoring of therapy aimed at managing hyperglycaemia-induced systemic toxicities.

Early and holistic intervention

Establishment interventionist's management routine for people identified with prediabetes. To achieve this; the study views 'holistic intervention' in diabetes pathogenesis from the perspective of public health as education, lifestyle changes and medical therapies. Further, the study defines lifestyle changes as involving the *knowledge, attitude and practice* (KAP) gap including possible adjustment to nutritional habits, exercise therapy, and emotional stress management.

Social work perspective

Establishment of a support system for social workers (including students) to be integrated in the prediabetes care team. This is with intent to emphasize the emotional stress management vis-à-vis psycho-social assessment and planning component of '*Early and holistic intervention*'. To achieve this, the study views 'support system' in diabetes pathogenesis from the perspective of complementary services to orthodox medical care provided to clients by physicians and other health service providers. Further, the study defines complimentary service as a consistent regular schedule of counseling follow up on client's wellbeing including but not limited to emotional and family impacts.

The proposed research design and methods

The plan is in three phases with the first phase involving screening for early identification of prediabetes and UDM and will run yearly for 5 years with option for continuity. Ethics and logistics are almost complete for data to be collected at three high schools and churches in Ndokwa West local government area of Delta state, Nigeria. In Australia, high schools, Charles Darwin University and plazas in Darwin will be approached for public health lectures and recruitment of volunteers from among individuals who are 18 year or older. POCT and a questionnaire will be used to screen for prediabetes

Table 1: Sample size projections

Phase	Activity	Centre*	Sample size (N)	Basis of projection
I	By screening	1 and 3	2000	N=400/year ×5 years
	From pathologies	2	N/A	
II	Identified prediabetes and undiagnosed diabetes	1 and 3	500	≈ 25%‡
		2	500	N/A
III	Progression to diabetes±CVD	1-3	120	≈ 12% PD/year†

*Centres: [1]Charles Darwin University, Darwin NT Australia, [2]Charles Sturt University, Albury NSW Australia, [3]Novena University, Ogume, Delta State Nigeria; ‡Prevalence of prediabetes depends on the criteria used.[33] The 25% projection here is based on impaired fasting glucose and speculation of increasing prevalence over the years.[7,34]; †It is estimated that up to 5-12% of prediabetes will develop type 2 diabetes each year.[6,7]

and CVD. The blood samples will be tested for, *e.g.* glucose and lipid levels and HbA1c and urinalysis as well as anthropometric measurements shall also be carried out. Questionnaire will seek to ascertain social (activity, smoking, alcohol consumption, *etc*) and history (DM, CVD, or blood pressure in family) factors. We anticipate to screen a sample size of 2000 of both genders by the end of 5 years of first the phase [Table 1].

The second and third phases will be a 5-10 years longitudinal study. Participants identified in the first phase as having prediabetes without dyslipidaemia, or clinically established CVD will be invited to participate in the longitudinal study. The second phase shall focus on preventive management of risk of progress to diabetes and explicit CVD. There have been controversies surrounding the use of antioxidants, or exercise in diabetes management. Therefore, data collection shall be as in the first phase; plus medical history and oxidative stress indices. OSP will be performed to verify oxidative stress as synonymous to smoking risk. Further, medical nutrition therapy and professional ''social work perspectives'' have yet to be fully incorporated in various aspects of healthcare. This arm of the study shall be carried out with a view to develop evidence-based guideline and suggest alternative appropriate strategy for intervention of systemic toxicities associated with prediabetes or undiagnosed diabetes progression. The use of antioxidants, exercise, and nutrition will therefore be evaluated.

The third phase, which will run *pari passu* with the second, will include follow-up to monitor the development of diabetes and CVD. This study is mindful of the fact that normally after school people may move for jobs or further education while others may relocate for different reasons hence some attrition is expected. In order to manage this on the 5 year follow up, participants would be requested to give telephone address, names, and contact details of close relative to be contacted in case of relocation.

From the tests that will be carried out, there is the expectation of finding that a participant is diabetic (previously unknown). Such participant will be referred to her/his general practitioner (GP) or health centre for management, while further consent to be followed-up in the study will be sought. An initial cross sectional study is going to be done in Nigeria to determine reference range for the Ndokwa community, which will be compared with the Australian values to make a definition for the study.

The third phase shall focus on two goals:

1. The primary objective is developing CVD risk assessment in prediabetes and undiagnosed diabetes. Diagnosis of prediabetes without co-morbidity shall be the baseline marker, and defined by fasting blood glucose. Clinically diagnosed diabetes mellitus with cardiovascular disease (DM+CVD) shall be the endpoint. Therefore, participants included in the prospective longitudinal study shall be followed for at least 5 years. The outcome of the follow up shall be dichotomous ''YES'' or ''NO'' DM+CVD.
2. A secondary objective is the development and validation of OSP for clinical evaluation of hyperglycaemia-induced systemic toxicities.

Significance

The research significance is ''DEAR'' for discrimination of health problem, education, adaptability, and relevance. The study proposal discriminates a health problem that individuals with prediabetes or UDM are overlooked in the existing heart disease screening in diabetes. Metabolic syndrome is a major risk factor for CVD, and associated with occupation. Hence, the need for regular surveillance and lifestyle interventions in occupational groups have been suggested.[35] The need to advance knowledge in diabetes has always been, such as the call for "attention to diet, glycemic control, metabolic stresses, and early diagnosis and monitoring of complications."[36] There is also poor patients' adherence with prescribed drug regimen, which is most probably due to poor knowledge and practice of successful self-management.[37] This study will contribute to education in the areas of (i) correlation and prevalence of metabolic syndrome in prediabetes, (ii) oxidative stress in metabolic stress associated with smokers, and (iii) self management, amongst others. The methodologies proposed to be used in this study are mostly standard clinical practice procedure, or readily adaptable. The relevance to primary and public health care is, obviously, early identification and intervention of cardiovascular risk among people who are otherwise categorized as "NO diabetes" and/or "Non-smoker."

Conclusion

This study intends to identify people with prediabetes and UDM and then follow them in a 5 years longitudinal study whereby the endpoint is development of DM and CVD co-morbidity. A model chart shall be developed for cardiovascular risk assessment in prediabetes and UDM. As part of intermediate research goals, free diagnostic screening service for early identification and intervention would be provided to the remote Ndokwa community of Nigeria and prevalence data will be submitted as fact sheets to the relevant health departments. Also as part of intermediate goals, attempt will be made to translate oxidative stress research in diabetes for clinical

practice; and the potential for management of stress in prediabetes will be explored with a view to establish counselling model and recommend same for clinical practice validation. Such efforts coupled with education shall empower the community, thereby reduce the prevalence/incidence of DM and CVD and the mortality and morbidity associated with these diseases that can be managed by timely and appropriate intervention.

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