Reflections on the WHO multinational study of vascular disease in diabetes (WHO MSVDD): an historical contribution from a unique study half a century on

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Introduction

The present “pandemic of diabetes mellitus” [1] calls for worldwide efforts to achieve control, including re-examination of the motives, methods and outcomes as well as the lessons learned in the course of a unique multinational study planned and carried through under the aegis of the Non-Communicable Division (NCD) of the World Health Organization (WHO) and with the assistance of the US National Institutes of Health. As we contemplate organized and systematic measures of prevention and management, some reflections on our experiences of almost half a century ago could be appropriate and useful.

Ideals and aims

In the 1950s, with the advent of oral antidiabetic agents, mainly sulfonylureas, vigorous discussion on their role in dealing with the complications of diabetes was generated,

especially in relation to the importance of attaining metabolic control. Much of the argument was drawn from experience with type 1 diabetes with increasing volumes of data suggesting that those poorly controlled on ‘free diets’ had more blindness, kidney failure and gangrene.

The controversial reports from the University Group Diabetes Program (UGDP) of adverse cardiovascular effects of the sulfonylurea tolbutamide in the very early 1970s [2] acutely raised the question of control and complications and methods of treatment in type 2 diabetic patients, and this question of the aggravated cardiovascular threat to people with diabetes and lesser degrees of glucose intolerance was a main subject of discussion of the visiting professorship to Tokyo in 1970 of one of us (HK).

This visit strongly impressed him with the major apparent differences in the relative impact of the large vessel (arterial) and the small vessel (microangiopathic) complications of diabetes between patients with ostensibly similar degrees of the metabolic disorder in London and Tokyo. In London diabetics, coronary heart disease and ischemic gangrene dominated the clinical picture; in Tokyo patients, these complications were relatively uncommon, with retinopathy and nephropathy most prominent [3].

In a taxicab discussion with another author (EM), also stimulated by a report in the previous year [4], it was agreed that a careful London/Tokyo comparison of macro- and microvascular complications in people with diabetes might be valuable. This proposal actually matured into the WHO multinational study. At first the idea was taken up and a potential study design developed by the European Diabetes Epidemiology Study Group. In due course, a working protocol emerged designed to make a standardized comparison of the impact of diabetic macro- and microvascular complications in carefully age/sex/duration-structured national samples from many nations around the world.

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Recruitment of research centers and preliminary meeting

Through a welcome commitment of interest by the non-communicable disease (NCD) section of WHO Geneva, groups interested in joining the study were voluntarily recruited worldwide. Those able to meet the moderately demanding entry requirements held a preparatory planning and training meeting in London in January 1974. At this, Kelly M. West, George Lynn Cross Professor at the University of Oklahoma [5], played an important initiating role. Finally, 14 centers from 13 countries were recruited to the study: London, Brussels, Switzerland, Berlin, Zagreb, Warsaw, Sofia, Moscow, New Delhi, Hong Kong, Tokyo, Arizona, Oklahoma and Havana. We were unable to recruit a white or black American cohort; the Oklahoma and Arizona US samples were composed of Native Americans. WHO Geneva NCD Section's successive Medical Officers, I. Glazunov, V. Khatchaturov, V. Grabauskas and M. Mitrofanov, and WHO biostatistician, Bernard Grab, played a central role as convenor, data collator and analyst in bringing this initial cross-sectional frequency study to a successful conclusion.

Recruitment using a pre-selection “cell-grid” concept

A detailed protocol was drafted in English to make the study as simple and objective as possible. Instructions, descriptions and questionnaires were next translated into local languages, then returned to WHO for back-translation by expert translators to make sure that original meanings were correctly conveyed.

In an effort to create a truly representative sample from each center, the selection was made from all outpatients who had attended the selected general hospitals or diabetes clinic in the previous year. Study patients were recruited from a $3 \times 3 \times 2$ grid in which age of enrollment, restricted to 35–55 years, was divided into three 7-year subgroups, as was the estimated duration of diabetes (i.e., <7, 7–14 and more than 14 years) for men and women separately.

From each age/duration/sex cell, 28 patients were randomly recruited to the study, aiming at the optimal total of 504 patients per center. In centers like Tokyo, where young onset diabetes is rare, there was serious difficulty in finding the required number of youthful onset, long-term patients. This was a general recruiting problem except in Switzerland where the sample was constructed by physicians countrywide.

On definitions used and standardization of results

After much discussion, we reached a pragmatic agreement to accept as diabetic patients who, after individual

consideration, were recognized as such by experienced staff in each center. Treatment details were recorded, and patients were classed as insulin-dependent when insulin was started within 1 year of diabetes diagnosis.

In some ethnic groups (e.g., native Americans), this was an unsatisfactory definition.

The body mass index (BMI) was adopted for the first time for use in a large international study. This index of obesity was originally created in 1835 by Quételet [6], an astronomer deeply interested in human behavior and social phenomena. He organized the first international conference of statistics in 1853.

Measures to improve reproducibility and comparability

Symptoms of angina pectoris and intermittent claudication were ascertained by the use of the Rose cardiovascular questionnaire [7], and all the 12-lead electrocardiograms from baseline and follow-up examinations were sent to London for independent Minnesota coding [8] by two experts. Blood and urine samples were deep-frozen and analyzed at a central laboratory, though some ‘politically sensitive’ samples had to be tested in WHO quality-controlled centers on the ‘other side’ of the Iron Curtain [9].

In contrast to well-validated ascertainment methods for arterial obstructive disease [10] or “macroangiopathy” (e.g., questionnaires, blood pressure and ECG), simple methods for documenting retinal and renal “microangiopathy” had not been established at the time of this study [11]. After debate, participating clinicians agreed on a detailed protocol for direct clinical ophthalmoscopy, and a simple, digital, descriptive coding for type and degree of diabetic fundus lesions. For nephropathy semiquantitative urinary protein analysis with a standardized version of the salicylsulfonic acid precipitation test was used to meet the needs of the most resource-limited societies.

Immunoassay for microalbuminuria was not yet well established, retinal cameras were unavailable to most centers, and validated methods for analysis and coding of fundus photographs evolved subsequently. Glycosylated hemoglobin measurement was still in its early investigative stage.

Results

Cross-sectional prevalence study

In our initial baseline study, we found large differences in macrovascular disease prevalence among centers. This held in respect of diagnostic symptomatology, ECG findings and lower limb amputation experience. In each, rates varied widely between countries. The lowest were found in the

Oriental samples and the highest among Europeans [10], confirming the a priori supposition that initiated the study.

Ischemic gangrene was rare in Oriental countries, especially in Tokyo, initiating a change in concept concerning foot pathology, i.e., from the assumption of a primarily ischemic to an essentially neuropathic etiology. As anticipated, diabetes duration was a major determinant of retinal and renal microangiopathic disease, and proportions of patients affected varied considerably among centers [11]. These differences, however, were not as large as those for macroangiopathic complications. The findings from ophthalmoscopy and urinalysis were supported by corresponding variations in rates of loss of visual and renal function among centers. Particularly at risk for both macro- and microvascular diseases were the Arizona Native American subjects of the study [12].

The 9-year protocol-based follow-up incidence study

Ten centers from nine countries were able to meet the strict requirements demanded for follow-up, namely: London, Switzerland, Warsaw, Berlin, Zagreb, Hong Kong, Tokyo, Arizona, Oklahoma and Havana.

Originally, a 10-year follow-up was planned, but world events including political unrest and population movements in Europe and Asia curtailed the study, and patient follow-up was completed on average 8.1 years following the baseline visits [13]. In all, 66.9% of the original patients were re-examined, though the shortfall was unavoidably largely attributable to loss of a third of the Zagreb sample and almost one-fifth of the Hong Kong patients. Losses from other centers were generally <3%.

For those who were alive but unable to attend for examination (15.2%), information was obtained through medical records and from their doctors and relatives.

For the deceased (11.4%) a copy of the death certificate was requested, supported when possible by additional clinical records.

Following the baseline survey, initial analysis of incidence rates was carried out at WHO Geneva. Subsequent follow-up data collection and analyses were skillfully and scrupulously carried out in the Epidemiology and Biostatistics Department of the University of Oklahoma by Prof. Kelly West and Prof. Elisa T. Lee, the latter taking sole responsibility after the untimely death of Kelly West. Generous support for this analytical phase and preparation for publication by the US National Institutes of Health is gratefully acknowledged.

Mortality

Cardiovascular disease accounted for 44% of the total mortality in insulin-dependent and 52% in non-insulin-

dependent patients. The relatively low cardiovascular mortality in the Japanese cohort has been interpreted as having important implications for potential reduction of cardiovascular mortality in people with diabetes in other parts of the world.

In general, the national incidence rate patterns of macrovascular disease events and deaths quite closely mirrored the comparative prevalence rates in the baseline study, and both mirrored, at a substantially higher level, the rates in their corresponding general non-diabetic populations. This was interpreted as demonstrating a 'diabetes-induced sensitization' to environmental atherogens, many of them potentially reversible.

The study underlined the importance of adiposity as a risk factor for macrovascular disease though, as in non-diabetic populations but with even greater impact, its effect was largely mediated through the accompanying raised arterial pressure and dyslipidemia.

Concerning microangiopathy, it is a matter of regret that the retinopathy study preceded the wide availability of retinal photography, which has proved of such great objective value. However, despite the inevitably lesser precision and greater observer variation, it is unlikely that this accounted for the larger part of the major differences in prevalence and the up to threefold differences in incidence observed. Strikingly in Tokyo, the low frequency of macrovascular disease contrasted markedly with the high prevalence of retinopathy, though the incidence was relatively low. Retinopathy prevalence and incidence were associated with a number of baseline risk factors, e.g., fasting plasma glucose, diabetes duration arterial pressure and triglyceride levels.

Problems with national sample collection

Switzerland was a special case. Internists and ophthalmologists of all the Swiss cantons participated in this study with the secretariat in Bern. With access to the whole nation in this way, all the sampling frame age/duration/sex "cells" could be filled with the required numbers. Swiss assiduity has to be applauded for the considerable toil involved in circulating protocols in all its four languages, in its effective sample collection and meeting costs of this national endeavor. Patients of other centers were, as the city names imply, recruited from outpatients of one or a few large clinics, apart from Havana and Warsaw where the sample was defined geographically in the city.

Methods developed since the 1970s and now routinely in use would have been of great value in improving precision and reproducibility of findings in this study, especially in respect to ascertainment of early diabetic eye and kidney disease. The application of semiquantitative assessment of retinal photographs has greatly improved the

precision of assessment of retinal status and disease progression, most clearly manifested in its use in the classic Diabetes Control and Complications Trial (DCCT). The quantitative assay of urinary albumin excretion rates at low concentrations (microalbuminuria) has also greatly improved understanding of early diabetic nephropathy. Although we found a surprising amount of correlative power of a single estimate of fasting blood glucose as a measure of baseline ‘diabetic control’ [14], the availability of glycated hemoglobin (HbA1c) measurement would have been a much better tool for its assessment. Simple and objective computerized methods for the digital fundus recording and analysis are urgently needed not only as an important research tool for epidemiologists and internists, but also for practicing physicians all over the world, despite the astonishing development in ophthalmological treatment of recent years.

Lessons for the future

As a long-term multinational follow-up study, the conduct and results of the WHO MSVDD present some useful lessons for the future.

The strong support of WHO NCD for the incidence study was very helpful. Though it provided no direct financial assistance, its involvement helped in raising national and local awareness and funding, and it generously provided facilities for the central computerized data collection and analysis (then in its relatively early stages) together with the venue for meetings. It is to be hoped that the WHO will lend continuing leadership in tackling similar opportunities for multinational studies in view of the growing world pandemic of diabetes.

Despite substantial advances in knowledge since the WHO MSVDD, the complications of diabetes—heart attack, stroke and gangrene, blindness, kidney failure and obstetric hazard—still impose heavy burdens on individuals, families and societies. We still need information drawn from well-constructed population studies from which we can learn more about the etiology, course and potential for prevention of these complications and, hopefully, ultimately, of diabetes itself.

Standardized, information-gathering, prospective studies in a number of very different populations, like the WHO MSVDD, are vulnerable to large, often unforeseeable

population movements like those that occurred in Croatia and Hong Kong during our follow-up study. However, as much is to be learned from differences between populations as from their similarities in respect of susceptibility to non-communicable disease like diabetes. A central agency with access to international expertise and internationally validated methods and procedures greatly facilitates the mobilization of research and preventive efforts to confront multinational threats to the public health.

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