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Collaborating with international clinical organizations

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ABSTRACT

The provision of quality laboratory services for patient care to improve healthcare outcomes is at the centre of the work of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). However the day to day work of laboratory medicine practitioners largely does not involve direct contact with patients. The IFCC Executive Board has therefore included in its strategic plan activities to highlight collaboration with clinical organizations.

A review of IFCC activities demonstrates a wide range of such collaborations with international health and clinical organizations at all levels. The IFCC Executive Board leads such collaborations with leading international bodies including the World Health Organization and World Association of Societies of Pathology and Laboratory Medicine (WASPaLM). The work of the Scientific Division has involved collaborations with 16 clinical organizations at the level of the Executive Committee as well as with specific Committees and Working Groups.

Furthermore in recent years the Executive Board has established a number of Task Forces with strong interaction with clinicians and clinical organizations. The harmonization of the assay for haemoglobin A1c is just one example of technological improvement to not only improve the performance of the test for monitoring disease but increase its utility for diagnosis which currently involves collaboration with clinicians.

The IFCC is continuing to expand its relations with international clinical organizations to enhance both the translation of developments in laboratory medicine to improve patient care and clinical outcomes and their adoption into clinical practice via inclusion in clinical guidelines.

INTRODUCTION

The provision of quality clinical laboratory services to improve patient care and healthcare outcomes is at the centre of the work of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Included in the Mission of the IFCC are statements highlighting this goal including working "to enhance the scientific level and the quality of diagnosis and therapy for patients throughout the world" as well as to "build on the professionalism of our members to provide quality services to patients." All of us working in Laboratory Medicine are conscious that direct contact with patients in our day to day work is unusual. Consequently the Executive Board of the IFCC has considered as a priority activities to enhance the Laboratory Medicine – Clinical interface, aiming to improve the efficacy of our practice and to facilitate the translation of developments in our field into patient care. Within the strategic plan of the 2012-2014 IFCC Executive Board were two goals: "Develop a plan to increase collaboration between IFCC and international clinical organizations" and "Establish at least one new collaboration each year with an international clinical organization".

In recent years the IFCC has advocated for laboratory medicine to adopt a strategy focussed on the patient to improve clinical effectiveness and outcomes through activities such as clinical interpretation and provision of advice on laboratory results. Furthermore, patients are increasingly taking more responsibility for their own health and are requiring such information to influence decisions on their healthcare. Models of healthcare delivery are changing with the integration of imaging and other sources of data into clinical guidelines improving knowledge to speed up healthcare and improve patient outcomes. One consequence of integrated diagnostics is the erosion of traditional boundaries within laboratory medicine and between diagnostic modalities.

THE RANGE OF IFCC CLINICAL COLLABORATIONS

The IFCC collaborates at the level of the Executive Board with international clinical organizations including the World Health Organization (WHO) and the World Association of Societies of Pathology and Laboratory Medicine (WASPaLM). Collaboration with WHO has increased particularly since this organization has recognised the increasing importance of non-communicable diseases for health throughout the world. Diabetes mellitus is one such disease and is becoming much more common in resource-limited settings. There has been an increased understanding of the improvement of clinical outcomes associated with effective monitoring of blood glucose and haemoglobin A1c (HbA1c) as well as significant changes to the diagnostic criteria for diabetes mellitus during the past decade. IFCC has pioneered the standardization of HbA1c measurement with considerable benefit to method comparability and the effective monitoring of diabetic patients. IFCC has also been working with WHO to revise a WHO booklet entitled 'Laboratory diagnosis and monitoring of diabetes mellitus' for the use of clinical and laboratory medicine specialists, especially in resource-limited settings.

Table 1 Clinical organizations collaborating with the IFCC Scientific Division

World Gastroenterology Organization
The International Association of Therapeutic Drug Monitoring and Clinical Toxicology
International Society of Endocrinology
American Thyroid Association
International Diabetes Federation
International Growth Hormone Society
European Association of Allergy and Clinical Immunology
International Osteoporosis Foundation

The IFCC Scientific Division has supervised a variety of clinical collaborations undertaken by their Committees and Working Groups over many years. These have included a wide range of clinical disciplines working on specific projects (Table 1). Current projects include the Working Group – Standardization of Albumin Assay in Urine (WG-SAU) working in collaboration with the US National Kidney Disease Education Program (NKDEP); Working Group – Standardization of Insulin Assays (WG-SIA) working in collaboration with the American Diabetes Association and the European Association of Diabetes Societies; Working Group – Standardization of Bone Marker Assays (WG-SBMA) working in collaboration with the International Osteoporosis Foundation; and the Task Force on Chronic Kidney Disease working in collaboration with WASPaLM, Kidney Disease Improving Global Outcomes (KDIGO) and Asia Forum for CKD Initiative. The IFCC has seven Task Forces working on integrated projects across the Scientific and Education and Management Divisions of the IFCC to which numerous clinicians have been appointed to provide expertise on the clinical translation of developments in laboratory medicine to improve healthcare outcomes.

CASE STUDIES ON IFCC CLINICAL COLLABORATIONS

1. Chronic kidney disease

Kidney Disease–Improving Global Outcomes (KDIGO) is a collaboration between the International Society of Nephrology, the Transplantation Society, a number of national nephrology societies, Canadian national organizations for health research and provision of clinical services and some pharmaceutical companies. In 2009 it held a conference to discuss the definition, classification and prognosis of chronic kidney disease where data from some 1,558,332 participants ranging across healthy subjects to high-risk subjects for kidney disease and patients suffering from kidney disease were subject to meta-analyses. Summaries of the data and the decisions arrived at from the congress were published (1).

The data indicated that both all-cause mortality and cardiovascular mortality were strongly inversely related to estimated-glomerular filtration rate (eGFR) and independently directly related to urine albumin excretion expressed as the albumin to creatinine ration (ACR). These data allowed for the derivation of clinically critical decision limits for these parameters.

For eGFR a value lower than 60 mL/min/1.73 m^2 was accepted because the hazard ratio for mortality increases sharply below this level. For urine albumin, cut-offs were adopted at less than 30 mg albumin per g creatinine, 30 to 300 mg/g and greater than 300 mg/g. These values were used to develop clinical guidelines for primary care medical practitioners as well as medical specialists.

Collaboration between IFCC WG-Glomerular Filtration Rate Assessment and NKDEP had ensured the development and adoption of a reference measurement procedure for creatinine in serum or urine utilizing isotope dilution-mass spectroscopy technology and standard reference materials for serum creatinine (2). By 2012 KIDIGO was able to recommend adoption of reporting eGFR for the assessment of kidney function for all patients calculated with the CKD-EPI formula (3) using serum creatinine assays aligned to the reference measurement procedure. Thus with the availability of appropriate clinical data, in collaboration with clinical laboratory professionals and the *in vitro* diagnostics industry, the highest level of clinical practice for the diagnosis and monitoring of chronic kidney disease can be made available to all patients through their primary care physicians.

The next step is to ensure the adoption of these practices internationally. In a number of countries or regions the leading nephrology and laboratory medicine organizations have come together to implement these recommendations. For example, in Australia and New Zealand the Australasian Creatinine Consensus Working group was established for such an implementation program. This involved nephrologists (through Kidney Australia) and laboratory medicine practitioners (through the Royal College of Pathologists of Australasia and the Australasian Association of Clinical Biochemists, the member society representing the region within the IFCC). Manuscripts were published in the Medical Journal of Australia, the official publication of the Australian Medical Association, reporting on automatic reporting of estimated glomerular filtration rate and clinical interpretation of results (4) as well as chronic kidney disease and measurement of albuminuria or proteinuria (5). Consequently Australasian clinical laboratories have adopted the following practices to ensure optimal treatment for diagnosis and monitoring of chronic kidney disease at all levels of medical practice but especially at the level of the primary care practitioner: standardized creatinine assays; common units for reporting creatinine and eGFR; universal reporting of eGFR; standardized interpretation of results; universal definition of CKD according to eGFR and urine albumin:creatinine ratio values; a link between laboratory results and interpretation and clinical management of the patient; and finally, communication of nephrology specialist advice to primary care practitioners via the clinical laboratory result report, allowing patients to receive the highest quality of medical treatment for CKD from their primary care physician close to their home.

While adoption of these recommendations is widespread across North America, Europe, Australasia and parts of Asia, in other regions such clinical collaborations have not yet occurred. Therefore the IFCC, in collaboration with WASPaLM, has established a Joint Task Force to help national organizations to implement best clinical practice guidelines for the management of CKD. At this level, a major obstacle is effective communication between all stakeholders. Ensuring traceability of creatinine assays to recognized international reference materials using reference measurement procedures has been adopted by the established major international *in vitro* diagnostic (IVD) equipment and reagent providers.

However, there are currently approximately 100 IVD companies who provide reagents and instruments for creatinine measurements in clinical laboratories and therefore there is considerable work to be done to ensure all these assays meet the quality requirements for optimal clinical care.

2. Postmenopausal osteoporosis

Osteoporosis is highly prevalent with some 50% of women and 30% of men over the age of 60 years expected to experience a fracture, which imposes considerable morbidity and premature mortality on our aging populations. Treatment of these fractures and their consequences, such as loss of the ability to live independently, results in the largest costs on healthcare budgets of any medical condition. The ability to identify patients at increased risk of fracture and those who are not responding to treatments would be a great benefit. Bone turnover markers have been in use in research settings and by medical specialists for over 50 years with the aim of identifying appropriate biomarkers. While many markers show promise, no consistent data have been generated from clinical research either to allow interpretation of bone turnover measurements for the individual patient at the level of the primary care physician or to permit bone turnover markers to be incorporated in clinical guidelines for osteoporosis. Recognizing the clinical importance of improving osteoporosis care, the International Osteoporosis Foundation (IOF) and the IFCC agreed to collaborate on investigations of the role of bone turnover markers, if any, in clinical management and a Joint Working Group between IOF and IFCC (WG-BMSO) was established.

The WG undertook the evaluation of current data and review of publications between 2000 and 2010 (6), aiming to recommend particular bone turnover marker assays for standard clinical practice. Some 7 bone formation marker assays are available for clinical laboratories as reagent kits or available on automated clinical chemistry platforms and 8 bone resorption marker assays are similarly available. Some clinical data suggested that these assays were useful for both prediction of fracture risk and for response to treatment. However there is significant variation between studies, and the data were largely of low quality and restricted to European populations. Therefore current data are inconclusive with regard to interpretation of assay results for the individual patient.

The WG concluded that it was necessary to enlarge the experience with a limited number of designated bone turnover marker assays for fracture risk assessment in population-based studies in subjects of a variety of ethnicities as well as for monitoring response to osteoporosis treatments. Furthermore, consensus was reached that there is no evidence identifying a perfect bone turnover marker. Criteria for an ideal marker have been delineated, including the following: adequately characterized biologically and chemically; anatomical specificity for bone; high performance in fracture risk prediction and in monitoring osteoporosis treatments among women and men; widely available on automated platforms and not the monopoly of a single supplier; assays to demonstrate suitable biological and analytical variability, sample handling, stability and ease of analysis; and finally, assays that are available for analysis from blood specimens. Two bone turnover markers, C-telopeptide fragments of collagen type 1 α1 chains, also known as serum Crosslaps (CTX-1), assayed in plasma or serum as an assessment of bone resorption, and N-terminal Propeptide of Type 1 Procollagen (P1NP) assayed in serum as an assessment of bone formation best met these criteria and were recommended to be assessed in all future clinical trials.

Between 2010 and 2011, the National Bone Health Alliance (a North American collaboration between clinical organizations involved with the clinical management of osteoporosis), pharmaceutical companies and organizations representing laboratory medicine (American Association of Clinical Chemistry) also conducted a review of the scientific literature (7). Their conclusions were similar, recommending collecting further clinical research data for the bone turnover markers CTX-1 and PINP.

Currently these assays are available on automated platforms from two manufacturers: Immunodiagnostics Systems Ltd (IDS) iSYS® and Roche Diagnostics Cobas®. If data from clinical trials are to be combined to conduct meta-analyses for assessment of the efficacy of bone turnover marker levels, the values generated by these platforms must be comparable. Currently for CTX-1 there are conflicting preliminary data, while data for PINP suggest that these values are comparable from the two systems. A second Joint Working Group between the IOF and the IFCC has been established to define the comparability of assays for CTX-1 and PINP (WG-SBMA) and to harmonize or standardize as feasible if they are not comparable. This project is currently underway in collaboration with the NBHA.

CONCLUSIONS

The IFCC is participating in a range of collaborations with clinical organizations based on specific projects. Such projects arise from developing requirements for optimal healthcare delivery and improved patient outcomes. For some well-established biomarkers clinical utility is being improved by, for example, standardization of the various assays used in clinical laboratories to ensure the optimal application of clinical guidelines based on critical levels for these biomarkers. The examples of serum creatinine and urine albumin for the diagnosis and assessment for the clinical management of chronic kidney disease are examples. For new biomarkers, the goal of these collaborations is the appropriate clinical application and development of clinical guidelines incorporating biomarker values. The use of cardiac troponins for the diagnosis of acute cardiac syndrome is an example. Other projects are working to establish the appropriate status of biomarker assays such that their clinical efficacy can be investigated. Bone turnover markers in the diagnosis and management of osteoporosis are an example of this activity.

The IFCC is actively promoting collaborations with clinical organizations to enhance the contribution of laboratory medicine in healthcare delivery, clinical effectiveness and patient outcomes. These goals are achieved through a patient-focussed strategy by increasing the quality of laboratory medicine practice to improve patient safety and clinical usefulness; ensuring the timely presentation of clinical laboratory results and provision of appropriate clinical interpretation and advice; and maintaining the financial sustainability of laboratory medicine by improving cost effectiveness, ensuring the appropriate use of the laboratory and providing value for money.

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