

Standardization in laboratory medicine: Adoption of common reference intervals to the Croatian population

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Abstract

Considering the fact that the results of laboratory tests

provide useful information about the state of health of patients, determination of reference value is considered an intrinsic part in the development of laboratory medicine. There are still huge differences in the analytical methods used as well as in the associated reference intervals which could consequently significantly affect the proper assessment of patient health. In a constant effort to increase the quality of patients' care, there are numerous international initiatives for standardization and/or harmonization of laboratory diagnostics in order to achieve maximum comparability of laboratory test results and improve patient safety. Through the standardization and harmonization processes of analytical methods the ability to create unique reference intervals is achieved. Such reference intervals could be applied globally in all laboratories using methods traceable to the same reference measuring system and analysing the biological samples from the populations with similar socio-demographic and ethnic characteristics. In this review we outlined the results of the harmonization processes in Croatia in the field of population based reference intervals for clinically relevant blood and serum constituents which are in accordance with ongoing activity for worldwide standardization and harmonization based on traceability in laboratory medicine.

Key words: Calibration traceability; Applicability of reference intervals; Harmonization and standardisation; External quality assessment; International Federation of Clinical Chemistry enzyme reference methods; Amino-transferase "common" reference intervals; Creatinine enzymatic method

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Core tip: The main goal of medical laboratories is to be able to support the clinicians with the best achievable quality in all laboratory results and reports. Ongoing evaluation and improvement processes are essential to ensure performance in compliance with the highest

professional and accreditation standards in order to provide optimal health benefit for the patient. In this review we outlined the results of the harmonization processes in Croatia in the field of population based reference intervals for clinically relevant biochemical constituents which are in accordance with an ongoing activity for worldwide standardization and harmonization based on traceability in laboratory medicine.

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INTRODUCTION

The population based reference intervals for healthy subjects are of outmost importance for the transversal clinical interpretation of laboratory test values^[1-4]. In spite of ongoing improvement processes there are still huge differences in the analytical methods used, as well as in the associated reference intervals which could consequently significantly affect the proper assessment of patient health^[5,6]. The International Organization for Standardization (ISO) standard 15189 require that "biological reference intervals shall be periodically reviewed"^[7], while according to the directive of the European Union on *in vitro* Diagnostics Medical Devices the manufacturers have to provide detailed information on reference intervals^[8].

Considering the fact that the results of laboratory tests provide useful information about physiological changes and the state of health of patients, determination of reference value is considered an intrinsic part in the development of laboratory medicine.

PRODUCTION OF POPULATION BASED REFERENCE INTERVALS IN CROATIA

Availability of the right interpretation of laboratory test results and reports is essential to ensure the optimum patient outcome. For this reason investigations of biological variation and the appropriate reference intervals for different clinically relevant biochemical constituents have been the subject of investigation of many laboratories, mostly throughout Western Europe and North America, over the last few decades. For the first time in our country the health associated reference intervals were produced for 34 blood and serum constituents according to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendations proposed by the Clinical Laboratory Standard Institute (CLSI) C28 document^[9] on the representative reference sample group of 2246 adults and 998 school children and adolescents, age 8-70 years, from the

territory of Zagreb and its surrounding, in the period from 1998 to 2000^[10-15].

Reference intervals for glucose, potassium, sodium, chloride, magnesium, iron, zinc, total proteins and electrophoretic fractions of total serum proteins, enzyme activities, total and low density cholesterol and triacylglycerols as well as for hematological and coagulation parameters were obtained by using nonparametric methods to estimate 2.5 and 97.5 percentiles of age and sex distribution as upper and lower normal reference intervals. Owing to related achievements, the Department of Medical Biochemistry and Laboratory Medicine at the University Hospital "Merkur" Zagreb, was designated by the Ministry of Health of the Republic of Croatia as the national Reference Center for the Production of Reference Values in the Field of General Medical Biochemistry in 2000. Today's activities of the Reference Centre are directed to harmonization of laboratory test results based on metrological criteria and traceability concept in laboratory medicine and validation of the applicability of the global "common" reference intervals to the Croatian population.

HARMONIZATION OF LABORATORY TEST RESULTS IN CROATIA

In order to contribute to the harmonization process of laboratory test results at the national level, in 2004 the Croatian Society of Medical Biochemists [Committee for External Quality Assessment (EQA) of MBLs], Croatian Chamber of Medical Biochemists and Department of Clinical Chemistry and Laboratory Medicine University Hospital Merkur-Reference centre of the Ministry of Health for the production of reference values in the field of general medical biochemistry have started the project of harmonization of laboratory test results for the following parameters: Metabolites and substrates, enzymes, electrolytes, microelements, proteins, routine urine analysis, complete blood count with differential and laboratory coagulation.

Project consisted of two main phases. The main goal of the first phase was to achieve analytical comparability of the tests results and reports between the medical biochemistry laboratories of the primary, secondary and tertiary level of medical care in Croatia based on implementation of recommended analytical methods. Second phase key goal was to achieve the highest possible level of clinical comparability of the test results by the application of the health associated population based reference intervals produced on representative reference sample group of Zagreb and its surroundings to all Croatian medical biochemistry laboratories.

The long-term evaluation of national EQA results in the period from 1998 to 2003 has shown that medical biochemistry laboratories use different analytical methods for the same analytes and that some of them were not able to fulfil the required analytical quality specification. For this reason, in the first phase of the project the

application of the same analytical methods for the routine blood and serum constituents in all medical biochemistry laboratories in Croatia was recommended. After applying recommended analytical methods and complying with established criteria for analytical quality of the results through the national program of EQA, conditions have been met for the second phase of the project - clinical comparability of obtained results. In 2005 the Croatian Chamber of Medical Biochemists recommended the use of health associated population based reference intervals produced on representative reference sample group of Zagreb and its surroundings to all Croatian medical biochemistry laboratories using the same analytical methods with acceptable performance evaluated through national EQA programme^[16,17]. For the paediatric population, unique reference intervals were recommended according to the literature data.

THE ROLE OF LONG TERM EVALUATION OF NATIONAL EQA IN HARMONIZATION OF REFERENCE INTERVALS IN CROATIA

Proficiency testing programs in Croatia have been continuously performed since 1973, by the Committee for EQA, which in 2012 outgrew in the CROQALM - Croatian centre for quality assessment in laboratory medicine conducted by the Croatian Society for Medical Biochemistry and Laboratory Medicine, a non-profit, non-governmental organization dedicated to operate a nationwide quality assessment in laboratory medicine according to the international standard for the providers of interlaboratory comparisons, ISO/IEC 17043:2010 - Conformity assessment - General requirement for proficiency testing, which was adopted as Croatian norm in 2010. Croatian Society for Medical Biochemistry and Laboratory Medicine as an independent organizer of the EQA of medical biochemistry laboratories, became a full member of European Organization For External Quality Assurance Providers in Laboratory Medicine (EQALM) in 1998. Many of Croatian medical biochemistry laboratories actively participate in international measurement evaluation projects in the field of medical biochemistry and post-analytical automated haematology under the auspices of EQALM in order to achieve a high degree of interlaboratory comparability and improve the analytical performance of laboratory tests required for patient care.

The national external quality assessment programme for medical biochemistry laboratories is formed modularly including laboratory tests in the field of medical biochemistry, laboratory haematology and coagulation, urinalysis, acid base status and ionized electrolytes, thyroid hormones, tumour markers and glycated haemoglobin and is organised three times per year. For acceptability of laboratory test results an internationally accepted hierarchical approach to analytical quality goals based on metrological principles, biological variation and

diagnostic needs is used. Certificate for the participation in the national EQA is issued annually to each laboratory.

The long-term evaluation of the obtained results presented in the publications in the relevant professional and scientific periodicals, workshops organised at the national congresses, symposia and meetings as well as presentations at the international meetings^[18-21] show that national proficiency testing programs have an important role in improving analytical quality and working conditions in the medical biochemistry laboratories in Croatia and became the basis of overall activities in the field of harmonisation of laboratory test results and transmission of the international recommendations into the national expert practice. The significant contribution to the interlaboratory comparability of the results comes also through the legislative regulations by Law on Medical - Biochemical Activities in 2003, according to which the participation of medical biochemistry laboratories in the national EQA programmes became mandatory.

Medical biochemistry laboratories in Croatia also participate in the different EQA schemes in the field of clinical chemistry, laboratory haematology and coagulation organized by international EQA providers: Labquality (World Health Organization Collaborating Centre for Education and Training in Laboratory Quality Assurance) Helsinki, Finland; United Kingdom National EQA Scheme for Haematology and Blood Coagulation; Sheffield, United Kingdom; Reference Institute for Bioanalytics Bonn, Germany; ECAT Foundation (External Quality control of diagnostic assays and tests with a focus on Thrombosis and Haemostasis) Amsterdam, The Netherlands; INSTAND e.V. (Society for Promoting Quality Assurance in Medical Laboratories e.V.), Düsseldorf, Germany in order to provide performance in compliance with the highest professional standards, reduce laboratory errors and improve patient safety as the most important priority in laboratory medicine.

GLOBAL STANDARDIZATION/ HARMONIZATION IN LABORATORY MEDICINE

In a constant effort to increase the quality of patients' care, laboratory diagnostics are of great importance. In this regard there are numerous international initiatives for standardization and/or harmonization of laboratory diagnostics in order to achieve maximum comparability of laboratory test results, because non-standardized and/or non-harmonized results can lead to diagnostic errors and thereby reduce patient safety^[22]. Consequently, the main impetus for standardization and/or harmonization in laboratory medicine is to increase patient safety, but other reasons include the regulatory requirements such as accreditation in laboratory medicine, as well as the benefits of information technology including the possibility of creating an electronic patient record^[22]. To achieve this result it is necessary to harmonize the entire

Table 1 Reference intervals for creatinine concentrations^[31]

Age (gender) group	Percentile value, $\mu\text{mol/L}$	
	2.5 th	97.5 th
Common reference intervals for global application		
Cord sera	46	86
Term neonates 0-14 d	27	81
2 mo - < 1 yr	14	34
1 yr - < 3 yr	15	31
3 yr - < 5 yr	23	37
5 yr - < 7 yr	25	42
7 yr - < 9 yr	30	48
9 yr - < 11 yr	28	57
11 yr - < 13 yr	37	63
13 yr - < 15 yr	40	72
Adult (males)	64	104
Adult (females)	49	90
Reference intervals in the reference sample group of Croatian population ($n = 240$)		
Adult (males)	54	107
Adult (females)	50	93

laboratory examination including analytical processes which are under the direct control of laboratory professionals as well as processes that are outside of such control such as request appropriateness as a part of pre-preanalytical processes and the correct use and interpretation of the obtained laboratory test reports as a most important part of post-postanalytical processes.

As part of the process of standardization of analytical methods and the establishment of reference measurement systems in laboratory medicine, in 2002 the Joint Committee for Traceability in Laboratory Medicine (JCTLM) was established in order to coordinate the activities of the International Bureau of Weights and Measures (Bureau International des Poids et Mesures), the IFCC, the International Laboratory Accreditation Cooperation, the organizers of EQA and the manufacturers of equipment and reagents [*in vitro* diagnostics (IVD)]^[22,23]. As a result of all these activities the JCTLM has created a database of accepted and available reference materials, reference analytical methods and accredited reference laboratories. In addition, despite the opinion of a part of the laboratory experts that the concept of measurement traceability could not be introduced in the area of laboratory medicine except in rare cases^[24], it was shown that the application of metrological traceability has a great practical potential and global value. This was confirmed through^[24]: The establishment of a reference measurement system (JCTLM); Development of analytical methods and related reagents (IVD) in accordance with traceability chain; Producing traceable, multicenter reference intervals; Introducing the commutable control samples in EQA schemes in order to objectively assess the level of achieved analytical accuracy; Defining target values for analytical methods used; Rejection of the application of non-specific methods of insufficient quality.

Through the standardization of analytical methods the ability to create unique reference intervals is

achieved. Such reference intervals could be applied globally in all laboratories using methods traceable to the same reference measuring system and analysing the biological samples from populations with similar socio-demographic and ethnic characteristics^[23,25].

For the complex analytes for which the laboratory test results often are not expressed in SI-, but in arbitrary units the concept of harmonization has been proposed based on the "Step-Up" design^[26,27]. This essentially comprises a sequence of method comparisons with selected sets of commutable samples. The outcome of each phase informs the decision as to whether the step-up to the next phase should be undertaken. The biggest disadvantage of this process is the limited amount of commutable clinical samples required to maintain the process of harmonization^[26,27]. In 2010, in order to launch international initiatives for the harmonization process in the laboratory medicine the International Consortium for Harmonization of Clinical Laboratory Results, (www.harmonization.net) based in the American Association for Clinical Chemistry was founded. This ensures a global infrastructure with the aim of defining a systematic approach to determining the list of the complex analytes for which there are no higher-order reference measurement procedures and for which it was unlikely that such procedures could be developed^[27] in order to increase patient safety through the best achievable quality and comparability of all laboratory test results.

APPLICABILITY OF COMMON REFERENCE INTERVALS FOR SERUM CREATININE CONCENTRATIONS TO THE CROATIAN POPULATION

In order to harmonize the serum creatinine results and their interpretation the applicability of recommended "common" reference intervals for creatinine concentrations was evaluated^[28-30]. Serum creatinine concentrations were measured using specific enzymatic method traceable to the IDMS method in comparison to the uncompensated Jaffe kinetic creatinine method^[31]. The representative reference sample group consisted of 240 healthy subjects who were "a priori" selected in accordance with the IFCC recommendation. The obtained results were almost identical as the recently recommended "common" reference intervals for global application by the IFCC Committee on Reference Intervals and Decision Limits^[32].

Based on the obtained results (Table 1) it is recommended that the "common" reference intervals could be used for creatinine measurement in all Croatian medical-biochemistry laboratories employing standardized, specific enzymatic method. The most important prerequisite is that their analytical performance meet the recommended performance goal of < 10% total error^[33-35]. According to the CLSI approved guideline, validation of reference intervals is advisable^[36].

The introduction of common reference intervals produced using specific enzymatic method should cause the disappearance of different intervals for creatinine results depending on the analytical method used which is in accordance with the National Kidney Disease Education Program recommended that estimated glomerular filtration rate has to be routinely reported along with specific serum creatinine measurements^[37-39].

TRANSFERABILITY OF ASPARTATE AND ALANINE AMINOTRANSFERASE COMMON REFERENCE INTERVALS TO THE CROATIAN ADULT AND PEDIATRIC POPULATION

According to the standardization of enzyme catalytic activity concentration measurements using IFCC reference methods and production of standardized reference intervals, the evaluation of the transferability of IFCC recommended "common" reference intervals for aspartate and alanine aminotransferase to the Croatian population was performed by the Department of Clinical Chemistry and Laboratory Medicine University Hospital Merkur-Reference centre of the Ministry of Health for the production of reference values in the field of general medical biochemistry, Zagreb, Croatia.

The reference group consisted of 120 healthy subjects (40 adults and 60 paediatric samples, between 1-19 years of age) selecting a posterior according to the strictly defined criteria. In standardised pre-analytical conditions the catalytic activity concentration for serum aspartate and alanine aminotransferase were measured using IFCC reference methods on the Beckman Coulter AU 680 biochemical analyser.

Analytical methods used in this study are accredited according to ISO 15189 and the results were confirmed through participation of the Department of Medical Biochemistry and Laboratory Medicine Merkur University Hospital in the International EQA schemes organized by Labquality WHO Collaborating Centre for Education and Training in Laboratory Quality Assurance, Helsinki, Finland. The reference intervals were validated as recommended by the CLSI^[36].

The obtained results showed that in age groups which represent the local adult healthy population, 18 to 20 subjects (95%-100%) were within the recommended IFCC common reference intervals for aspartate as well as for alanine aminotransferase catalytic activity concentration. The obtained results for paediatric samples showed that 18 to 20 subjects (95%-100%) were within the evaluated reference intervals for the group between 10 to 12 years of age. In the age group between 13-19 years 55% to 65% of results were within the evaluated reference intervals while the other results were below the reference intervals. Verification of reference intervals for aminotransferases for Croatian adult and pediatric patients using IFCC recommended

analytical methods in comparison to previously produced reference intervals recommended by Croatian Chamber of Medical Biochemists in 2007, are presented in Tables 2 and 3 together with related references^[10,14,15,40-44].

The obtained results confirmed that the IFCC recommended common reference intervals for aspartate and alanine aminotransferase activity concentrations are appropriate for the adult Croatian population. The verification of reference intervals for the paediatric population obtained with IFCC recommended reference methods have to be confirmed with multiple local validations in order to become widely used^[45].

In 2014, as a part of the ongoing harmonisation project the Croatian Chamber of Medical Biochemists has recommended specific enzymatic method to be used as routine analytical method for the measurement of serum creatinine concentrations and IFCC recommended methods for the measurement of aspartate aminotransferase and alanine aminotransferase activity concentrations. Based on the evaluation of the reference intervals and verification studies application of "common" reference intervals to the Croatian population was recommended. The results of these long-term evaluation and improvement processes as well as interlaboratory variability of the obtained results are clearly demonstrated through national EQA program which is obligatory for all medical biochemistry laboratories and is one of quality indicators in scope of the external professional audit of medical biochemistry laboratories in Croatia.

CONCLUSION

Since the process of standardization and/or harmonization give a very important contribution to raising the overall quality of laboratory diagnostics and thus significantly improves the level of health care of patients, it is necessary to constantly encourage this process through the active involvement of manufacturers, regulatory authorities, the organizers of EQA and medical and laboratory experts.

The highest priority in laboratory work in this process is to constantly raise the level of patient safety, thus reducing the risk of possible laboratory error that can adversely affect the process of treatment or be the cause of possible fatal outcome^[46]. In this respect the introduction of quality management system according to international standard ISO 15189 in clinical laboratories gives a strong contribution to the timely elimination of all potential errors that could compromise the safety of patients and supports preventive measures and activities to resolve possible errors and to ensure the desired outcomes of treatment. The International Standard ISO 15189 has been accepted as Croatian norm in 2003. Accreditation of medical laboratories is carried out on voluntary basis by the Croatian Accreditation Agency (HAA) which has a full membership in European co-operation for Accreditation. Up to now HAA has accredited 8 medical biochemistry laboratories in the

Table 2 Verification of reference intervals for alanine amino-transferase for Croatian patients

Analyte	Method	Unit	Reference interval			Ref.	Verification (%)
			Sex	Age (yr)	Interval		
ALT	Photometry UV, IFCC method, 37 °C, TRIS buffer, L-alanine, α -ketoglutarate, pyridoxal phosphate, NADH, lactate dehydrogenase, pH 7.15: CCMB recommendation for the Croatian population	U/L	Male, female	0-2	11-46	[40]	
			Male, female	3-7	9-20	[40]	
			Male, female	8-12	11-37	[10,15]	
			Male	13-19	10-33	[10,15]	
			Female	13-19	10-29	[10,15]	
			Male	≥ 20	12-48	[14]	
			Female	≥ 20	10-36	[14]	
	IFCC reference measurement procedure (IFCC RMS), IFCC IRMM reference material ERM-AD454 (2002): Common multicentric reference intervals for the adult population, 2010	U/L	Male	18-85	9-59	[41]	96
			Female	18-85	8-41		96
	Pediatric reference intervals						
	CALIPER, Canada, 2012; IFCC reference measurement procedure, Abbott Architect		Male, female	0 < 1	5-51	[42]	
			Male, female	1 < 13	11-30		90
			Male	13 < 19	10-33		55
			Female	13 < 19	8-24		65
	Denmark (NORIP), 2012; IFCC reference measurement procedure, Roche Modular		Male	5-8	8-27	[43]	
			Male	9-13	8-37		
			Male	14-18	8-47		
			Female	5-18	8-32		
	Germany (a posteriori, ambulance and hospital populations) 2009; IFCC reference measurement procedure, Roche Modular		Male, female	0-1	< 49	[44]	
			Male, female	1-3	< 29		
			Male, female	4-6	< 39		
			Male, female	7-12	< 44		
			Male	13-17	< 51		
		Female	13-17	< 45			

ALT: Alanine amino-transferase; IFCC: International Federation of Clinical Chemistry and Laboratory Medicine; CCMB: Croatian Chamber of Medical Biochemists; IRMM: Institute for reference materials and measurements; RMS: Reference measurement system; CALIPER: Canadian laboratory initiative on pediatric reference intervals.

Table 3 Verification of reference intervals for aspartate amino-transferase for Croatian patients

Analyte	Method	Unit	Reference interval			Ref.	Verification (%)
			Sex	Age (yr)	Interval		
AST	Photometry UV, IFCC method, 37 °C, TRIS buffer, L-aspartate, α -ketoglutarate, pyridoxal phosphate, NADH, malate dehydrogenase, lactate dehydrogenase, pH 7.65: CCMB recommendation for the Croatian population	U/L	Male, female	0-2	26-75	[40]	
			Male, female	3-7	24-49	[40]	
			Male, female	8-12	14-39	[10,15]	
			Male	13-19	11-38	[10,15]	
			Female	13-19	14-32	[10,15]	
			Male	≥ 20	11-38	[14]	
			Female	≥ 20	8-30	[14]	
			IFCC reference measurement procedure (IFCC RMS), IFCC IRMM reference material ERM-AD457 (2002): Common multicentric reference intervals for the adult population, 2010	U/L	Male, female	18-85	11-34
	Pediatric reference intervals						
	CALIPER, Canada, 2012; IFCC reference measurement procedure, Abbott Architect	Male, female	1 < 7		26-55	[42]	100
		Male, female	7 < 12		22-41		96
		Male	12 < 19		18-40		96
		Female	12 < 19		17-33		96
	Denmark (NORIP), 2012; IFCC reference measurement procedure, Roche Modular	Male, female	5-18		17-46	[43]	
	Germany (a posteriori, ambulance and hospital populations) 2009; IFCC reference measurement procedure, Roche Modular	Male, female	0-1		< 77	[44]	
		Male, female	1-3	< 71			
		Male, female	4-6	< 53			
		Male, female	7-12	< 48			
		Male	13-17	< 42			
Female		13-17	< 44				

AST: Aspartate amino-transferase; IFCC: International Federation of Clinical Chemistry and Laboratory Medicine; CCMB: Croatian Chamber of Medical Biochemists; IRMM: Institute for reference materials and measurements; RMS: Reference measurement system; CALIPER: Canadian laboratory initiative on pediatric reference intervals.

Republic of Croatia.

The introduction of standardized analytical methods reduces interlaboratory differences and requires the production of standardized, traceable reference intervals through multicenter studies with a large number of reference individuals, which should reflect only possible ethnic differences between the examined populations. The implementation of such population based reference intervals to the local population based on verification studies will significantly improve the quality of interpretation of laboratory results on a global level resulting in optimal health benefits for the patient.

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