Reference intervals for 25 of the most frequently used properties in clinical chemistry

Proposal by Nordic Reference Interval Project (NORIP)

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Introduction

A project for establishing common Nordic reference intervals for 25 of the most common properties used in clinical chemistry (table 1) was established 27th Mars 1998. The project was supported by The Scandinavian Society for Clinical Chemistry (NFKK) and the project members were elected by the national societies of clinical chemistry in the five Nordic countries: Peter Felding, Denmark (secretary), Leifur Franzson, Iceland, Veli Kairisto, Finland, Per Hyltoft Petersen, Denmark, Pål Rustad, Norway (leader), Gunnar Skude, Sweden. The project member from Sweden have since changed first to Kristoffer Hellsing, then to Per Simonsson.

Detailed project data are presented on the project home site (1).

General concept

Nordic laboratories were invited to participate to follow this general concept:

- Contribute 3500 DKR to the project group for the whole project.
- Collect at least 25 reference person (healthy personal and their healthy adult family members) serum-, plasma- and full blood samples (see "Inclusion criteria") and freeze at –80°C. The reference persons should be evenly distributed on gender and age. Some of the samples should be collected for analysis at the laboratory and some for submission to a central data bank (7 serum, 2 plasma, 1 EDTA buffy coat, each 1 mL). Each reference person should fill out a questionnaire to collect relevant data for evaluation of reference intervals.
- Receive 5 control materials on dry ice: CAL, X, HIGH, LOW, P. CAL (with reference method values for most properties) will be the "calibrator" of the project and X is produced for future use with transferred target values (both are unmodified frozen serum pools from male blood donors). HIGH (serum pool concentrated by freeze drying) and LOW (HIGH diluted 1:2 with an aqueous solution of sodium and calcium) will be used to evaluate linearity of methods and P (serum pool from women using oestrogen) as a general control with somewhat different properties than the other pools.
- Analyse controls (ten CAL and three of each of the other in at least one series and ten X in the rest of the series if necessary) and samples in one series at the laboratory. All labs were asked to analyse on thawed samples. The labs were also encouraged to do measurements on fresh serum and plasma with controls in series as described above.
- Submit analytical data, method data and reference person data to a central database.
- Reference intervals will be computed centrally.
- After project is finished, the bio- and data bank will be administered by The Scandinavian Society for Clinical Chemistry (NFKK).

Inclusion criteria for reference persons

The reference individual should

- be feeling subjectively healthy
- have reached the age of 18
- not be pregnant or breast-feeding
- not have been an in-patient in a hospital nor have been subjectively dangerously ill during the last month
- not have consumed more than 2 measures of alcohol (24 g) in the last 24 hours
- not have given blood as a donor in the last five months
- not have taken prescribed drugs other than the P-pill or estrogens during the last two weeks
- not have smoked in the last hour prior to blood sampling

Sample handling

Condition of reference person

The reference person should sit at least 15 minutes

[1] Nomenclature of "Committee on Nomenclature, Properties and Units (IFCC&IUPAC)" have been used in the text.

before sample collection. The sample should be collected with standard technique from the cubital vein with as little stasis as possible.

Sample collection

Heparin- and EDTA sample tubes should be mixed by turning the sample tubes ten times. The sample tubes, if possible, should be stored in the dark not to influence bilirubin concentrations.

After sample collection the primary tubes without addition should be kept at room temperature $^1/_2$ - $1^1/_2$ hours before centrifugation and Li-heparin tubes should be centrifuged within 15 minutes in room temperature. The samples should be centrifuged 10 minutes (minimum 1500g).

The serum samples should be distributed to secondary sample tubes within two hours after sample collection, plasma within half an hour. The samples should be stored at –80°C within four hours after sample collection.

Analysis

Before analysis the samples should be thawed at room temperature in the dark for one hour, then mixed by turning ten times. The measurements should be done within 4 hours after thawing of samples.

If fresh samples are used for analysis, this should be done within four hours after sample collection.

Data

Data collected from participating laboratories

Analytical method: Instrument manufacturer, instrument name, method group, method name, unit, slope and intercept ($V_S = V_i$ x slope + intercept where V_S is submitted value and Vi is original instrument value).

Reference person data registered on questionnaire: Person ID, age, gender, height, weight, date of 1. day of last menstrual period (women), ethnic origin, heredity for diabetes, number of years residing in a Nordic country, chronic disease(s), medication, strenuous exercise last week, alcohol consumption, habitual smoking, number of hours from the last meal, date of blood sampling, number of total blood donations.

Control analytical data: Control ID, measurement date, series no, measurement value.

Reference person analytical data: Person ID, measurement date, series no, material (serum or plasma), material handling (fresh or thawed), measurement value.

Data base

The data are stored in a MS Access relational data base at Fürst Medical Laboratory, Oslo and is administered by Pål Rustad.

102 laboratories have participated resulting in about 200 000 measurement data; about 125 000 reference values (of which barely half is on thawed serum) from 3036 reference persons and about 75 000 control values.

Data handling

The enzymes and the non-enzymes are treated differently:

Enzymes

Heidi Steensland, and later the Norwegian enzyme group (see "Evaluation") have had the responsibility to select the methods with necessary quality (compatible to IFCC methods at 37°C). If the laboratory have used a slope/intercept correction to the submitted data, the data have been transformed back to original instrument values.

Non-enzymes

For each series the reference values are multiplied with the factor Target CAL / Mean CAL in that series (or Target X / Mean X if only X have been used in that series).

Target values for reference sera

The target values for CAL is established in three different ways depending on component (see table 1):

1. Transferred value from IMEP 17-1 (2) to CAL by The Nordic Trueness Project, 2002.
2. Reference method values established in 1997 by DGKC[2].
3. Median from all laboratories in NORIP (HDL-cholesterol and TIBC)

The target value for X is either established as transferred value from IMEP 17-1 in The Nordic Trueness Project or as transferred value from CAL in NORIP.

Data exclusion

Data have been excluded for different reasons:

[2] DGKC: "Deuche Gesellschaft für Klinische Chemie".

(Fortsættes side 14)

Component	Unit	CAL		Quality goal			Calculated				
							Serum				
		Target value	Source	Bias	Gen-der	Age	Low	90% CI	High	90% CI	N
Albumin	g/L	40,52	NTP	2,1 %	FM	18-39	36,5	36.3-36.7	47,9	47.5-48.4	1010
						40-69			45,4	45.2-45.6	1248
						>=70	34,4	33.5-34.8			450
Bilirubin	umol/L	8,5	DGKC	6,6 %	FM	>=18	4,7	4.5-5.0	24	23.1-25.1	2738
Calcium	mmol/L	2,266	NTP	1,4 %	FM	>=18	2,17	2.17-2.18	2,51	2.50-2.52	2569
Calcium corrected	mmol/L	2,2816		1,2 %	FM	18-49	2,20	2.19-2.21	2,47	2.46-2.48	1385
						>=50			2,53	2.52-2.54	1149
Cholesterol	mmol/L	4,90	NTP	3,0 %	FM	18-29	2,89	2.78-3.04	6,18	6.0-6.37	674
						30-49	3,43	3.28-3.55	6,92	6.77-7.19	843
						>=50	4,02	3.98-4.14	7,87	7.73-8.09	1216
Creatinin	umol/L	70,6	NTP	4,7 %	F	18-59	51,1	50.2-52.0	84,1	83.0-87.0	1081
						>=60					310
					M	18-59	63,6	62.8-64.3	100,0	98.7-101.8	926
						>=60					317
Iron	umol/L	21,16	NTP	5,4 %	F	18-49	9,2	8.9-9.6	33,7	33.0-34.4	2309
Iron saturation		0,311		10,1 %	F	18-49	0,11	0.08-0.12	0,50	0.48-0.58	162
						>=50	0,14	0.11-0.17			133
					M	>=18	0,16	0.14-0.17	0,57	0.53-0.61	369
Glucose	mmol/L	4,464	NTP	1,7 %	FM	>=18	3,98	3.94-4.09	5,99	5.90-6.13	918
					F	>=18	3,94	3.86-4.05	5,87	5.68-5.99	482
					M	>=18	4,17	4.08-4.24	6,21	5.96-6.50	436
HDL-cholesterol	mmol/L	1,331	NORIP	3,9 %	F	>=18	1,03	0.99-1.06	2,61	2.54-2.66	1379
					M	>=18	0,83	0.79-0.86	2,13	2.05-2.16	1222
Potassium	mmol/L	3,74	NTP	2,3 %	FM	>=18	3,61	3.60-3.63	4,64	4.61-4.66	2608
LDL-cholesterol	mmol/L	2,9		4,0 %	FM	18-29	1,24	1.06-1.33	4,29	3.98-4.38	275
						30-49	1,39	1.28-1.68	4,71	4.39-5.11	310
						>=50	1,98	1.86-2.16	5,35	5.13-5.67	579
Magnesium	mmol/L	0,797	NTP	2,6 %	FM	>=18	0,71	0.70-0.71	0,94	0.93-0.95	2123
Sodium	mmol/L	137,4	NTP	0,5 %	FM	>=18	136,7	136.3-136.9	144,8	144.5-145.1	2642
Phosphate	mmol/L	1,03	DGKC	5,4 %	F	>=18	0,85	0.84-0.87	1,49	1.45-1.50	1365
					M	18-49	0,75	0.73-0.77	1,63	1.57-1.70	670
						>=50			1,33	1.31-1.39	558
Protein	g/L	67,1	DGKC	2,1 %	FM	>=18	62,4	62.0-62.7	77,9	77.5-78.8	1985
TIBC	umol/L	68,0	NORIP (IFCC transferrin)	4,8 %	FM	>=18	48,9	48.5-50.1	83,4	81.1-85.7	668
Triglycerides	mmol/L	1,31	DGKC	7,1 %	FM	>=18	0,47	0.44-0.48	2,60	2.35-2.86	1203
Urea	mmol/L	4,8	NTP	7,9 %	F	18-49	2,66	2.47-2.71	6,41	6.09-6.71	761
						>=50	3,11	2.97-3.31	7,97	7.66-8.35	585
					M	18-49	3,24	3.08-3.31	8,16	7.97-8.42	649
						>=50	3,64	3.46-3.78			538
Uric acid	umol/L	290,2	NTP	7,2 %	F	18-49	154	148-159	350	340-365	780
						>=50			394	379-414	608
					M	>=18	231	225-239	475	466-481	1232

NORIP Reference intervals

Plasma (Li heparin)					Suggestions: Serum		Suggestions: Plasma		
Low	90% CI	High	90% CI	N	Low	High	Low	High	Comment
35,8	35.2-36.3	47,2	46.9-48.1	452	36	48			
		45,4	45.1-45.9	589		45			
34,5	33.8-34.9			244	34				
5,1	4.7-5.4	26	24.3-28.4	887	5	25			
2,15	2.14-2.16	2,48	2.47-2.50	1204	2,15	2,51			
2,17	2.16-2.18	2,46	2.45-2.49	623	2,17	2,47			=Ca+0.020x(41.3-Alb) where 41.3 g/L
		2,52	2.49-2.53	558		2,53			is the albumin median
2,95	2.79-3.14	5,89	5.78-6.52	316	2,9	6,1			
3,35	3.13-3.51	6,75	6.41-7.06	368	3,3	6,9			
3,89	3.79-4.01	7,35	7.22-7.62	618	3,9	7,8			
50,5	47.4-52.7	87,5	84.5-90.4	647	50	90			See table 3 and plot of enzymatic-, Vitros - and Jaffe methods on NORIP
62,4	60.7-63.7	100,7	98.6-103.1	597	60	100			home site (1)
9,0	8.3-9.4	33,7	32.2-35.0	1076	9	34			Results <6 umol/L removed
0,12	-	0,61	-	56	0,10	0,50			Oestrogen users and iron <6
					0,15				umol/L removed
0,14	-	0,59	-	80		0,57			
4,18	4.14-4.36	6,29	6.12-6.52	527	4,0	6,0	4,2	6,3	Fasting (>=12 h)
4,13	3.97-4.18	6,12	5.91-6.30	271					
4,47	4.34-4.55	6,54	6.19-6.99	256					
1,04	0.98-1.08	2,68	2.59-2.79	644	1,0	2,7			
0,80	0.75-0.85	2,14	2.09-2.28	586	0,8	2,1			
3,47	3.45-3.49	4,38	4.32-4.43	1172	3,6	4,6	3,5	4,4	See table 2
1,21	0.58-1.36	4,00	3.68-4.30	144	1,2	4,3			
1,47	1.16-1.61	4,25	3.95-4.95	159	1,4	4,7			LDLchol.=cholesterol-HDLcholesterol-trigly-
1,94	1.73-2.05	5,08	4.89-5.86	351	2,0	5,3			cerides/2, where triglycerides is <4 mmol/L
0,71	0.71-0.72	0,93	0.93-0.94	943	0,71	0,94			
136,7	136.35-137.11	143,6	143.4-143.9	1291	137	145		144	
0,76	0.72-0.78	1,41	1.37-1.45	618	0,85	1,50	0,76	1,41	
0,71	0.69-0.73	1,53	1.45-1.59	298	0,75	1,65	0,71	1,53	
		1,23	1.16-1.31	271		1,35		1,23	
64,3	63.8-64.9	79,5	79.2-80.0	877	62	78	64	79	
47,4	44.7-49.8	79,8	76.0-84.5	136	49	83	47	80	Oestrogen users removed
0,45	0.42-0.48	2,39	2.21-2.55	704	0,45	2,60			Fasting (>=12 hours)
2,59	2.36-2.72	6,24	5.76-6.79	276	2,6	6,4			
3,05	2.68-3.38	7,40	7.23-8.70	248	3,1	7,9			
3,21	2.97-3.50	8,08	7.50-8.87	252	3,2	8,1			
3,46	3.24-3.61	8,06	7.83-9.75	230	3,5				
160	142-168	365	333-407	280	155	350			
		421	397-456	257		400			
227	213-235	482	455-502	503	230	480			

Component	Unit	CAL		Quality goal			Calculated				
							Serum				
		Target value	Source	Bias	Gender	Age	Low	90% CI	High	90% CI	N
Enzymes (7)											
Alanine aminotransferase	U/L	17,8	DGKC	6,1 %	F	>=18	8	6.7-8.5	46	43-49	1220
					M	>=18	10	8.9-10.9	68	63-74	1080
Aspartate aminotransferase	U/L	23,6	NORIP	3,4 %	F	>=18	13	12-13	37	35-38	1128
					M	>=18	14	13-15	45	43-47	1012
Creatinekinase	U/L	118,8	DGKC	7,3 %	F	>=18	33	31-35	207	180-233	1048
					M	18-49	50	45-54	398	351-487	397
					M	>=50	39	36-46	277	252-415	404
Alkaline phosphatases	U/L	64,0	NORIP	4,5 %	FM	>=18	37	36-39	106	101-113	954
Gamma-glutamyl-transferase	U/L	35,8	NTP	6,1 %	F	18-39	10	9-11	42	34-54	283
					F	>=40	11	10-11	77	64-81	445
					M	18-39	12	10-13	78	56-168	244
					M	>=40	15	14-16	114	99-134	409
Total amylase	U/L	55,4	NORIP	6,4 %	FM	>=18	27	25-29	118	113-124	719
Pancreatic amylase	U/L	27,0	NORIP	7,6 %	FM	>=18	11	6-13	64	54-68	497
Lactate dehydrogenase	U/L	141	NORIP	2,7 %	FM	18-69	103	90-106	204	198-210	372
						>=70	114	-	255	-	87

(Fortsat fra side 11)

1. Insufficient control data for reported reference values.
2. Same samples measured by different methods on same component.
3. Material difference: Automatic test of extreme differences between combinations of serum, plasma, fresh, thawed - the extreme value is excluded.
4. Person exclusions (exclusion criteria): Extreme values for one or more properties for one person excludes all results for that person:
   1. Glucose > 11 mmol/L, glucose > 7 mmol/L and fasting ≥ 12 hours
   2. 5s/3s and 4s/4s rule: At least one result outside median(NORIP) ± 5s for one property and at least one value for a different property outside median(NORIP) ± 3s (5s3s rule). The same rule have also been applied with 4s limits for both properties (s is total biological variation based on reference intervals from Malmø/Odense, logaritmic transformations).
5. Method exclusions: Not compatible with enzyme IFCC 37°C-methods, UIBC reported as TIBC method, ionised calcium reported as total calcium method, plasma with bad correlation with serum for some methods.
6. Component specific exclusions: Non-fasting (triglycerides, glucose), diabetes in near family (glucose), physical activity (CK), oestrogen use (TIBC), values <6 umol/L iron (iron and iron saturation).
7. Enzymes: Results outside mean + 4s (s - standard deviation of gender partitioned distributions using log-transformations).
8. Refval 4.0: Automatic exclusions for non-enzymes (see "Calculation of reference intervals").

Calculation of reference intervals

Method

Simple nonparametric method have been used to calculate low and high reference limits as 2.5 and 97.5 percentiles respectively of distribution of reference values, and calculations have been done by using computer program Refval 4.0 (3) based on IFCC recommendations.

Partitioning

Partitioning of distribution of reference values have been evaluated using theory outlined by Ari Lahti et al.

NORIP Reference intervals									
					Suggestions				
Plasma (Li heparin)					Serum		Plasma		
Low	90% CI	High	90% CI	N	Low	High	Low	High	Comment
7	6-8	45	37-50	482	10	45			
10	9-11	68	56-87	443		70			
14	13-14	36	34-38	533	15	35			
16	16-17	45	43-52	480		45			
35	32-36	215	192-257	473	35	210			Results for persons participated in
55	49-62	481	308-738	175	50	400			strenuous sports during the last week
42,0	42-46	405	261-475	200	40	280			before sample collection is excluded
44,0	35-48	95	90-113	141	35	105			Roche Modular and Vitros for serum and only Vitros for plasma
9,0	-	42	-	113	10	45			
9,0	3-10	77	61-92	206	10	75			
11,0	-	117	-	104	10	80			
13,0	10-14	109	72-127	185	15	115			
24	20-29	115	99-122	311	25	120			
11	8-13	61	49-71	218	10	65			Only Roche Modular
-		-		0	105	205			
-		-		0	115	255			

(4) and incorporated by him in Refval 4.0. The criteria for not partitioning is that >0.9% and <4.1% of each of the subdistributions should be outside 2.5- and 97.5 percentiles of the common distribution.

Conclusions on gender partitioning were mostly made using this program. Reasonable age limits have been estimated by 'qualified guessing' before partitioning program have evaluated the resulting subdistributions according to the criteria mentioned above.

Reference intervals

Evaluation of reference intervals

Seven groups from different laboratories in Norway have evaluated the reference intervals proposed by the NORIP project group for all properties as presented on the project home site (1). The results of the evaluation were presented at a one-day meeting on 7th April 2003 in Oslo. Most of the suggestions from the groups (reports on project home site) have been taken into account in the proposal presented below.

Proposed reference intervals

The proposed reference intervals are presented in table 1

Explanations to the column labels:

"Value": Reference method values used for CAL to correct reference values.

"Source": NTP: Transferred value from IMEP 17-1 in Nordic Trueness Project, 2002. DGKC: Reference method value from DGKC, 1997. NORIP: Median of CAL-values in NORIP.

"Quality goal": The percentages are calculated for each component as 0.375 of total biological variation calculated from reference intervals in this table as [log(H) – log(L)]/4 for lognormal distributions or as 0.5*(H-L)/(H+L) for normal distributions where H (high reference limit) minus L (low reference limit) is the most narrow suggested reference interval for that property.

"LOW" and "HIGH": Low and high reference limit.

"Gender": F-female, M-male

"Calculated": The reference limits and 90% confidence intervals (90% CI) in most cases are given with one decimal more than is reasonable to use in practice.

"N": Number of reference values used to calculate reference interval.

Discussion

Potassium

Table 2: Serum and plasma potassium reference intervals from different sources

	NORIP	Tietz (5)	Laurell (6)
Serum	3.5-4.6	3.5-5.1	3.5-5.0
Plasma	3.4-4.4	3.4-4.4	3.5-4.5

The upper reference limit for serum potassium is markedly lower than Tietz and Laurell suggests, but this is not the case for plasma. As the lower reference limit is essentially the same for serum and plasma for NORIP, Tietz and Laurell, but not the upper limit, this difference probably have something to do with sample treatment after collection. It might be assumed that sample treatment have been optimal in this project (see "Sample collection") relative to what is common in general practice.

Creatinin

Plots of the creatinin reference value distributions for male and female for the three major method groups Jaffé, Vitros (Ortho) and enzymatic are shown on the project home site.

Enzymes

See (7).

Documentation

Results from the project have been continuously updated on the project home site (1). Specific details for each property can be viewed by selecting the specific property from the table presented by selecting "Preliminary project data" and "Compiled data for each component".

Implementation of common reference intervals

Validation of method

To use the common reference intervals in Nordic laboratories the NORIP project group suggests that the quality goal should be that the laboratory's absolute value of bias relative to target value for the control X (or CAL) should be less than 0.375 of total biological variation, i.e. $|M/T - 1| < B$ where M is the measured value of X (or CAL) in the laboratory, T is the CAL target value and B the bias quality goal. B is presented in table 1 for each component in the column "Quality goal".

For the enzymes and some other components with low target values for CAL and X it might be necessary also to validate the method with respect to trueness at the levels of the reference limits.

On the project home site comparisons between serum and plasma for different instruments/instrument manufacturers are presented. These comparisons should be taken into account before reference intervals for plasma are taken into use.

The control serum X (NFKK Reference Serum X) will be available from DEKS[3].

NOBIDA (Nordisk Reference Interval Projekts Biobank og database)

The intention with establishing the bio-bank is to let other projects use the samples for establishing Nordic reference intervals for other properties than described here. NFKK has established a group that on their behalf will have the responsibility to handle requests for data and samples from the NFKK data- and bio-bank NOBIDA. The leader for the group is Pål Rustad. Guidelines for requests will soon be published on the internet home site of NORIP and at the NFKK home site (http://nc.ibk.liu.se/nfkk/head.htm).

The bio-bank including the control X, is located at DEKS.

Table 3: Creatinin reference intervals with 90% confidence limits for the three method groups.

	Female			Male		
	Reference interval	90% confidence interval	N	Reference interval	90% confidence interval	N
Enzymatic	46-92	41-50, 86-96	137	60-105	57-64, 101-109	113
Jaffé	52-84	51-53, 83-87	944	64-98	62-65, 96-100	858
Vitros	50-81	49-52, 79-83	298	64-102	63-66, 99-105	259
NORIP suggestion	50-90			60-100		

[3] Danish Institute for External Quality Assurance for Laboratories in Health Care, Denmark (http://www.deks.dk/)

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