Original Article

Within-subject biological variation in disease: collated data and clinical consequences

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Abstract

Quantitative data on the components of biological variation (BV) are used for several purposes, including calculating the reference change value (RCV) required for the assessment of the significance of changes in serial results in an individual. Pathology may modify the set point in diseased patients and, more importantly, the variation around that set-point. Our aim was to collate all published BV data in situations other than health. We report the within-subject coefficient of variation (CV_I) for 66 quantities in 34 disease states. We compared the results with the CV_I determined in healthy individuals and examined whether the data derived in specific diseases could be useful for clinical applications. For the majority of quantities studied, CV_I values are of the same order in disease and health: thus the use of RCV derived from healthy subjects for monitoring patients would be reasonable. However, for a small number of quantities considered to be disease specific markers, the CV_I differed from those in health. This could mean that RCV derived from healthy CV_I may be inappropriate for monitoring patients in certain diseases. Hence, disease-specific RCVs may be clinically useful.

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Introduction

The biological variation (BV) of quantities examined in laboratory medicine can be described as of three types, namely, variation over the span of life, predictable cyclical variation that can be daily, monthly or seasonal in nature, and random variation.[1] Most quantities have random biological variation.

Within-subject or intra-individual biological variation is the average random fluctuation around the homeostatic set point of individuals. Between-subject or inter-individual biological variation is defined as the difference between the set-points of individuals. In mathematical terms, these are usually expressed as coefficients of variation (CV) and termed CV_I and CV_G, respectively.[2] The method for estimating the components of BV, based on nested analysis of variance (ANOVA), has been fully described.[1,2] Briefly, a number of samples are obtained from each of several subjects strictly following a predetermined protocol. The most important conditions that are required include the following:

- the health status of the subjects must be known;
- pre-defined exclusion criteria must be applied;
- the pre-examination phase of the process should be standardized with regard to the subject preparation, sample collection and storage until examination procedures are performed;
- analytical variability during the testing process should be minimized; and
- the data obtained should be statistically dissected into analytical, within-subject and between-subject components using ANOVA following exclusion of outliers through appropriate statistical methodology.[1,2]

Quantitative data on the components of BV are used for several purposes, including setting analytical quality specifications,[3] determining the number of samples required to establish an estimate of the homeostatic setting point of an individual,[4] assessing the utility of population-based reference intervals[5] and calculating the reference change value (RCV) required for the assessment of the significance of changes in serial results in an individual.[6–8]

It has become common practice to use RCVs estimated from healthy subjects to detect significant changes in the status of patients. However, the underlying pathology may modify the set-point in diseased patients and, more importantly, the variation around that set-point. If this is true, the use of RCVs from healthy subjects may not be the most appropriate strategy for this task. CV_I estimated from individuals with a specific disease may be more suitable for calculation of RCV that would be of value in interpretation of serial results in patients with that particular disease. Some preliminary work examining this hypothesis has been done in patients who have undergone renal replacement therapy with the aim of early detection of rejection and other crises,[9] and in patients with chronic liver disease with the aim of detection of early hepatocellular carcinoma.[10] These studies, the first to apply BV data derived from patients with chronic stable disease in monitoring, have shown that this approach allows the detection of changes in the clinical condition of patients before they manifest clinically.

Many authors have published collated data on the components of BV. Several years ago we compiled data derived from healthy subjects in a database that includes the BV components for numerous quantities in healthy subjects. Several versions of this information for healthy subjects, including the most recent update, are available in publications and on the Internet.[11–14]

BV in diseased subjects has been the subject of various studies in recent years. Although the available information is still limited, as can be seen by the relatively small number of studies dedicated to this subject and compiled in the database appended to this work, we considered it sufficient to perform a preliminary analysis to assess whether our hypothesis, that disease specific RCVs would be useful, was tenable. Our aim in this review was to collate published BV data in situations other than health. We report the CV_I stratified by disease and compare the results with the CV_I determined in healthy individuals and examine whether the data derived in specific diseases might be useful for clinical applications.

Material and methods

The data collected were retrieved from articles in the literature that had the specific stated aim of determining the components of BV. The system used to select the papers and to determine the reliability of the information retrieved in the overall assessment of BV components in health and disease has already been described in detail.[11–14] In summary, each source was read independently by two of the authors of the present study to determine its suitability for inclusion. The criteria for rejection of a paper were as follows:

- the components of BV were obtained indirectly, that is, the study was not specifically designed to estimate these; and
- the mathematical model used to estimate the components of BV was not based on ANOVA and therefore not considered robust.

For each quantity in each disease situation the following data were collated:

- the components of BV, particularly CV_I;
- the matrix studied;
- the number of subjects studied;
- the duration of the study, expressed in days;
- the number of samples collected from each subject;
- the disease; and
- the mean value and the units used in expression of the data.

All papers compiled deal with patients in a stable clinical situation, except those relating to acute myocardial infarction.

To facilitate examination, the quantities studied in the various diseases were first listed in alphabetical order. Then, for each quantity, the literature CV_I values were classified in ascending order. These values were then compared to those from healthy subjects. When numerical differences were observed, we reassessed the literature to investigate if such differences could be attributed to any other factors recorded, such as the number of subjects studied, time period covered or number of samples collected per subject. In addition, we noted whether the diseases were in acute or chronic phases.

To illustrate this procedure, the data for alkaline phosphatase (ALP) provide an example. This quantity was studied in three diseases. In two of them, the CV_I values were of the same order as the median found in the many studies on healthy subjects, whereas in the third, it was two-fold higher. Inspection of the other data recorded disclosed the following:

(1) the number of subjects studied were similar in the disease with ALP activities similar to the conventional population-based reference interval compared to that with activities two-fold higher;

(2) the lengths of study were similar in diseases with very dissimilar CV_I, the number of samples studied were similar in all three diseases;
(3) the disease states were all chronic rather than acute.

Hence, influences of these factors on the differences observed were ruled out and it was considered that the differences were real.

Results

The database contained information from 66 quantities estimated in 34 diseases, obtained from 45 papers published in 15 scientific journals. The subjects studied were from several countries and continents. The biological matrices analyzed were mainly serum, and less often urine and sweat. Thirty-nine quantities were each examined in a single study, and 27 appeared in more than one study. Serum potassium and sodium, the most frequently studied quantities, were each examined in eight articles.

The results obtained in each paper, organized by quantity and disease, are shown in Appendix 1.

Discussion

In laboratory practice, the data derived from components of BV in healthy individuals have been used as guides for medical decision-making in disease. However, prior to the present study there was no collated information to clarify whether BV data in health and disease were similar.

We found that CV_I in disease were, in the majority of cases, of the same order as those in healthy individuals. These data could not be submitted to rigid statistical comparison to determine significant differences because of the small number of measurements available for each quantity and the heterogeneity of the study designs and methods compiled.

For quantities not considered to be biochemical markers for the specific disease studied, the distribution of data was within the distribution of healthy CV_I values. For example, serum sodium, one of the quantities for which the largest number of studies was available, showed CV_I values between 0.6% and 1.5% with a median of 0.8% in disease (healthy distribution: 0.3% to 2.0%, median 0.7%). Since such small differences would have no effect on clinical applications, it would not be necessary to calculate disease specific RCV in most clinical situations. This is an important finding because it means that much larger amount of data on the components of BV documented for healthy individuals can generally be used, as advocated previously,[2] in chronic stable disease states.

Nevertheless, some CV_I values were found to be higher, but markedly so in only seven organ specific diseases, namely:

- α-fetoprotein, for which the CV_I in hepatic diseases was higher than that of healthy subjects; nevertheless it was identical to the usual in colon cancer;
- ALP, for which the CV_I was higher in Paget's disease although in chronic renal failure and chronic liver disease it was almost identical to the CV_I in health;
- CA 125, for which the CV_I was higher in ovarian cancer (specific marker for this disease);
- CA 15.3, for which the CV_I for this typical breast cancer marker was higher in patients with this disease than in healthy subjects;
- carcinoembryonic antigen, for which the CV_I was higher in most studies of patients with colorectal cancer;
- creatinine, for which the CV_I was higher in kidney disease and post-transplantation than in healthy subjects; and
- haemoglobin A1c, lipoprotein (a) and first morning urine albumin showed higher CV_I in patients affected by diabetes mellitus than in healthy subjects.

In these few cases, it might be that the use of a RCV calculated from the healthy state might be lower than appropriate for the specific clinical situation and this could result in 'false positive' signals for a patient being monitored. This could lead to an inappropriate medical decision, such as an unnecessary increase in the treatment dose, with consequent risk of toxicity or unnecessary invasive testing, as well as the negative psychological impact of a positive result on the patient.

The findings from this preliminary overview of the current situation regarding the CV_I in disease and the limited clinical application of the RCV concept in laboratory medicine lead us to suggest that estimation of disease-specific RCVs should be further investigated for key quantities used in patient monitoring in well defined conditions with established clinical follow-up protocols. Initial efforts in studies by Biosca *et al.*[9] in renal post transplantation and Trapé *et al.*[10] in hepatocellular carcinoma have shown promise in the detection of changes in the disease status before clinical manifestations are evident. In addition, a recent paper from Solétormos *et al.*[15] provides an excellent example of the use of BV concepts in interpreting serial total prostate specific antigen concentrations in prostate cancer.

Conclusions

CV_I values in a number of disease states are provided in this collation of the available data. For the majority of

quantities studied, CV_I values are of the same order in disease and health: thus the use of RCVs derived from healthy subjects for monitoring patients would be reasonable. However, for a small number of quantities considered to be disease specific markers, the CV_I differed from those in health. This could mean that, rarely, RCVs derived from healthy CV_I may not be appropriate for monitoring patients in certain diseases. Hence, disease specific RCVs may be clinically useful. Further studies focused on specific, well documented disease states could be warranted in the light of this study.

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Appendix 1 *Collated data on biological variation in disease states. Median CV_I values for each quantity in healthy individuals, obtained as explained in the compilation of our database,[11,13,14] are included for comparison*

Quantity	Matrix	CV_I (%) Healthy (median)	CV_I (%) Disease	n	d	s	Disease	Ref	Mean	Units
α-Fetoprotein	S	12	12	30	180	3	Colon neoplasm	10	2.86	μg/L
α-Fetoprotein	S		35	40	180	3–10	Hepatic disease, no cirrhosis	10	4.07	μg/L
α-Fetoprotein	S		38	85	180	3–10	Hepatocellular carcinoma	10	3.97	μg/L
α-Fetoprotein	S		40	45	180	3–8	Cirrhosis	10	3.83	μg/L
Alanine aminopeptidase	S	4.1	4.3	20	28	7	Chronic liver disease	29	1.39	μkat/L
ALT	S	24	11	20	28	7	Chronic liver disease	29	2.04	μkat/L
ALT	S		13	27	56	8	Type I- DM	27	0.52	μkat/L
ALT	S		25	9	2	11	Impaired renal function	23	0.21	μKat/L
Albumin	S	3.1	2.8	16	56	8	Type I- DM	27	44	g/L
Albumin	S		2.9	8	21	8	Chronic renal failure	28	41	g/L
Albumin	S		3.3	20	28	7	Chronic liver disease	29	39	g/L
Albumin	S		4.3	9	2	11	Impaired renal function	23	39.1	g/L
Albumin	S		6.7	20	4	19	Acute myocardial infarction	22	37.1	g/L
Albumin, first morning	U	36	42	47	21	3	Type I-DM	39	350	mg/L
Albumin, first morning	U		61	16	21–28	10	Diabetic subjects	33	14	mg/L
Albumin/creatinine ratio	U	NA	39	16	21–28	10	Diabetic subjects	33	1.25	mg/mmol
ALP	S	6.4	6.4	8	84	8	Chronic renal failure	28	3.21	μkat/L
ALP	S		6.6	20	28	7	Chronic liver disease	29	7.5	μkat/L
ALP	S		12.4	15	72	5	Paget disease	17	9.8	μkat/L
ALP bone isoform	S	6.2	4.9	15	72	5	Paget disease	17	136	μg/L
Amino-terminal proBNP	P	NA	8.6	37	1	6	Stable chronic heart failure	20	570	ng/L
Amino-terminal proBNP	P		20	37	5	5	Stable chronic heart failure	20	570	ng/L
Amino-terminal proBNP	P		35	37	42	15	Stable chronic heart failure	20	570	ng/L
Amylase	S	12	8.2	17	21	8	Chronic renal failure	28	110	U/L
Amylase	S		8.4	20	28	7	Chronic liver disease	29	8.7	U/L
Amylase	S		11.1	27	56	8	Type I- DM	27	4.58	U/L
Amylase (total) first morning	U	NA	35	47	21	3	Type I- DM	39	4.58	μkat/L
Amylase (pancreatic) first morning	U	NA	38	47	21	3	Type I- DM	39	2.90	μkat/L
Amylase	Saliva	NA	51	47	21	3	Type I- DM	39	1.60	μkat/L
Apo-A1	S	6.5	7.1	143	70	3	Lipid disorders	36	1.50	g/L
Apo-B	S	6.9	6.4	143	70	3	Lipid disorders	36	1.71	g/L
AST	S	12	10.6	20	28	7	Chronic liver disease	29	1.76	μkat/L
AST	S		12.3	37	56	8	Type I- DM	27	0.48	μkat/L
Bicarbonate	S	4.8	7.9	20	4	19.5	Acute myocardial infarction	22	19.5	mmol/L
BNP	P	NA	8.2	37	1	6	Stable chronic heart failure	20	135	ng/L

Appendix 1 *Continued*

Quantity	Matrix	CV_I (%) Healthy (median)	CV_I (%) Disease	n	d	s	Disease	Ref	Mean	Units
BNP	P		24	37	5	5	Stable chronic heart failure	20	135	ng/L
BNP	P		40	37	42	15	Stable chronic heart failure	20	135	ng/L
CA 125	S	29	21.8	12	120	4	Non small cell lung carcinoma	43	NA	NA
CA 125	S		36.0	24	1095	5	Resected lung neoplasm (not oat cell)	36	10.6	U/L
CA 125	S		46.2	41	1095	7	Resected ovarian neoplasm	35	8.8	U/L
CA 15.3	S	6.2	7,0	50	30	3	Radically resected breast cancer	24	16	U/mL
CA 15.3	S		11.2	33	2010	11	Breast cancer (resected)	32	NA	NA
CA 15.3	S		16.7	170	90	NA	Breast cancer	25	16.2	U/mL
CA 19.9	S	16	24.5	41	1095	7	Resected ovarian neoplasm	35	8.8	U/L
CA 19.9	S		24.5	24	1095	7	Resected lung neoplasm (not oat cell)	35	13.2	U/L
Calcium	S	1.9	1.3	8	84	8	Chronic renal failure	28	2.34	mmol/L
Calcium	S		1.6	14	56	8	Hypertension	30	2.34	mmol/L
Calcium	S		2.8	9	84	11	Chronic renal failure	28	2.23	mmol/L
Calcium	S		4.8	20	4	19.5	Acute Myocardial infarction	22	2.25	mmol/L
Calcium	S		6.7	9	2	11	Impaired renal function	23	2.4	mmol/L
Calcium/creatinine ratio, 2 h	U	NA	33	46	2	2	Inpatients Metabolic bone disease	45	0.31	mmol/mmol
Calcium/creatinine ratio, 2 h	U		39	20	30–90	2	Outpatients Osteoporosis (only)	45	0.48	mmol/mmol
Calcium/creatinine ratio, 2 h	U		41	20	2	2	Inpatients Osteoporosis (only)	45	0.31	mmol/mmol
Calcium/creatinine ratio, 2 h	U		44	46	30–90	2	Outpatients Metabolic bone disease	45	0.39	mmol/mmol
CEA	S	13	9.8	92	30	3	Radically resected breast cancer	24	NA	NA
CEA	S		10.6	12	120	4	Non small cell lung carcinoma	43	NA	NA
CEA	S		12.4	31	900	3 to 7	Colon neoplasm	21	1.80	μg/L
CEA	S		16.2	420	90	>3	Radically resected breast cancer	24	NA	NA
CEA	S		19.1	32	901	4 to 7	Breast cancer (no evidence of disease)	21	1.40	μg/L
CEA	S		23.6	24	1095	5	Resected lung neoplasm (not oat cell)	35	1.77	mg/L
CEA	S		26.9	170	90	NA	Breast cancer (operated)	25	1.60	μg/L
CEA	S		27.0	33	2010	11	Breast cancer	32	NA	NA
CEA	S		44.9	33	1095	7	Resected colorectal neoplasm	35	1.99	mg/L
Chloride	S	1.2	1.1	14	56	8	Hypertension	30	105	mmol/L
Chloride	S		1.1	9	2	11	Impaired renal function	23	104	mmol/L
Chloride	S		1.8	41	90	8	Renal post-transplantation	18	108.6	mmol/L
Chloride	S		1.8	8	21	8	Chronic renal failure	28	110	mmol/L
Chloride	S		1.9	27	56	8	Type I-DM	27	100	mmol/L
Chloride	S		2.2	20	4	20	Acute myocardial infarction	22	102.7	mmol/L
Chloride	S		3.2	10	28	7	Chronic liver disease	29	103	mmol/L
Cholesterol	S	6.0	4.7	35	28	4	Mild hypercholesterolemia	41	6.0	mmol/L

Appendix 1 *Continued*

Quantity	Matrix	CV_I (%) Healthy (median)	CV_I (%) Disease	n	d	s	Disease	Ref	Mean	Units
Cholesterol	S		5.0	128	70	3	Lipid disorders	35	6.1	mmol/L
Cholesterol	S		5.2	20	28	7	Chronic liver disease	29	5.0	mmol/L
Cholesterol	S		7.0	14	56	8	Hypertension	30	6.0	mmol/L
Cholesterol	S		7.2	27	56	8	Type I-DM	27	5.6	mmol/L
Cholinesterase	S	7.0	7.1	20	28	7	Chronic liver disease	29	103	μkat/L
Creatine kinase	S	23	43	9	2	11	Impaired renal function	23	75.2	U/L
Creatinine	S	4.3	5.3	17	21	8	Chronic renal failure	28	483	μmol/L
Creatinine	S		5.9	27	56	8	Type I-DM	27	73	μmol/L
Creatinine	S		6.4	9	2	11	Impaired renal function	23	190	μmol/L
Creatinine	S		6.5	11	56	8	Type I-DM	27	64	μmol/L
Creatinine	S		11.5	41	90	8	Renal post-transplantation	18	148	μmol/L
Creatinine	S		13.0	54	540	9	Children chronic kidney disease	40	52	μmol/L
Creatinine	S		13.4	20	4	19.5	Acute myocardial infarction	22	85	μmol/L
Creatinine, first morning	U	NA	34	47	21	3	Type I-DM	39	10.1	mmol/L
CTx	S	9.6	12.4	15	365	5	Paget	17	5976	pmol/L
CTx/creatinine ratio, 2 h	U	NA	24	15	365	5	Paget	17	484	μg/mmol
Cyfra 21.1	S	22	21.8	12	120	4	Non small cell lung carcinoma	43	NA	NA
Cystatin C	S	NA	12	54	540	9	Children chronic kidney disease	40	2.81	mg/L
δ-ALA/creatinine ratio	U	20	20	15	70	10	Acute intermittent porphyria	16	6.9	μmol/mmol
δ-ALA/creatinine ratio	U		20	15	720	15	Acute intermittent porphyria	16	6.7	μmol/mmol
FT4	S	7.6	5.7	12	0.33	5	Primary hypothyroidism	19	NA	NA
FT3	S	7.9	8.7	12	0.33	5	Primary hypothyroidism	19	NA	NA
GGT	S	14	4.7	20	28	7	Chronic liver disease	29	6.8	μkat/L
GGT	S		9.9	27	56	8	Type I-DM	27	0.37	μkat/L
Glucose	S	5.7	27.4	9	2	11	Impaired renal function	23	5.1	mmol/L
HDL-Cholesterol	S	7.1	7.1	128	70	3	Lipid disorders	36	1.36	mmol/L
HDL-Cholesterol	S		7.7	27	56	8	Type I-DM	27	1.53	mmol/L
HDL-Cholesterol	S		8.7	14	56	8	Hypertension	30	1.07	mmol/L
HDL-Cholesterol	S		9.5	17	21	8	Chronic renal failure	28	1.00	mmol/L
Haemoglobin	B	2.8	2.3	14	56	8	Hypertension	30	9.8	mmol/L
Haemoglobin	B		2.9	27	56	8	Type I-DM	27	10.1	mmol/L
Haemoglobin	B		4.2	20	28	7	Chronic liver disease	29	8.9	mmol/L
Haemoglobin A1c	B	1.9	4.3	47	720–1260	4–7	Type II-DM	42	6.5	%
Haemoglobin A1c	B		8.8	214	365	4	Type I-DM	34	11.7	%
Hydroxyproline/creatinine ratio, 2 h	U	26	33.8	20	30–90	2	Osteoporosis (only)	45	30	μmol/mmol
Hydroxyproline/creatinine ratio, 2 h	U		40.6	46	30–90	2	Metabolic bone disease	45	37	μmol/mmol

Appendix 1 *Continued*

Quantity	Matrix	CV_I (%) Healthy (median)	CV_I (%) Disease	n	d	s	Disease	Ref	Mean	Units
Hydroxyproline/creatinine ratio, second	U	13	18.7	15	365	5	Paget's disease	17	200	nmol/mg
LDL-Cholesterol	S	8.3	6.6	35	28	4	Mild hypercholesterolaemia	41	4.30	mmol/L
LDL-Cholesterol	S		7.8	128	70	3	Lipid disorders	36	4.12	mmol/L
LDL-Cholesterol	S		9.5	85	365	4	Coronary artery disease	37	NA	NA
Lipoprotein (a)	S	8.5	26.2	12	360	4	Type I- DM	26	25	mg/dL
Lipoprotein (a)	S		23.3	24	360	4	Type I- DM	26	>40	mg/dL
Lipoprotein (a)	S		42.3	13	360	4	Type I- DM	26	15*	mg/dL
Lipoprotein (a)	S		42.3	21	360	4	Type I- DM	26	<10	mg/dL
MCA	S	10.1	14.9	33	2010	11	Resected breast cancer	32	NA	NA
NAG, first morning	U	NA	58	47	21	3	Type I-DM	39	48	nkat/L
NTx/creatinine ratio, 2 h	U	17	15.8	15	365	5	Paget	17	248	nmol
PBG, first morning	U	15	18.0	15	70	10	Acute intermittent porphyria	16	5.0	μmol/mmol
PBG, first morning	U		25.0	15	720	15	Acute intermittent porphyria	16	5.0	μmol/mmol
Potassium	S	4.8	4.5	14	56	8	Hypertension	30	4.36	mmol/L
Potassium	S		4.8	16	56	8	Type I- DM	27	4.65	mmol/L
Potassium	S		5.1	17	21	8	Chronic renal failure	28	4.98	mmol/L
Potassium	S		7.0	11	56	8	Type I- DM	27	4.81	mmol/L
Potassium	S		7.1	41	90	8	Renal post-transplantation	18	4.46	mmol/L
Potassium	S		7.7	20	28	7	Chronic liver disease	29	4.50	mmol/L
Potassium	S		12.4	20	4	19.5	Acute myocardial infarction	22	3.68	mmol/L
Potassium	S		13.3	9	2	11	Impaired renal function	23	4.5	mmol/L
Procollagen (Type I N-terminal)	S	6.8	10.0	15	72	5	Paget	17	176	μg/L
PAP	S	NA	34	15	4	8	Prostate cancer	38	6.7	U/L
PAP	S		34	15	4	8	Prostate cancer	38	0.8	U/L
PAP	S		34	15	4	8	Prostate cancer	38	0.3	U/L
PSA (total)	S	18.1	14	5	4	8	Prostate cancer	38	40.3	μg/L
PSA (total)	S		14	5	4	8	Prostate cancer	38	10.8	μg/L
PSA (total)	S		14	5	4	8	Prostate cancer	38	3.2	μg/L
PSA (total)	S		20	890	90–960	2–10	Prostate cancer	15	0.1–20†	μg/L
Protein, total	S	2.7	3.3	17	21	8	Chronic renal failure	28	74	g/L
Protein, total	S		4.1	27	56	8	Type I-DM	27	73	g/L
Protein, total	S		4.2	20	28	7	Chronic liver disease	29	78	g/L
SCC	S	39	39	24	1095	5	Lung neoplasm (not oat cell)	35	1.01	mg/L
Sodium	S	0.7	0.6	14	56	8	Hypertension	30	143	mmol/L
Sodium	S		0.7	17	21	8	Chronic renal failure	28	142	mmol/L

Appendix 1 *Continued*

Quantity	Matrix	CV_I (%) Healthy (median)	CV_I (%) Disease	n	d	s	Disease	Ref	Mean	Units
Sodium	S		0.8	27	56	8	Type I-DM	27	140	mmol/L
Sodium	S		0.8	9	2	11	Impaired renal function	23	142	mmol/L
Sodium	S		0.9	20	28	7	Chronic liver disease	29	140	mmol/L
Sodium	S		1.0	8	21	11	Chronic renal failure	28	143.4	mmol/L
Sodium	S		1.1	41	90	8	Renal post-transplantation	18	141	mmol/L
Sodium	S		1.5	20	4	19.5	Acute myocardial infarction	22	139.8	mmol/L
Sweat chloride	Sweat	15	7.3	20	35	5	Cystic fibrosis	44	120	mmol/L
T_3	S	8.7	8.4	13	56	8	Pregnancy	31	2.96	nmol/L
T_3	S		8.7	12	0.33	5	Primary hypothyroidism	19	NA	NA
T_4	S	4.9	4.9	12	0.33	5	Primary hypothyroidism	19	NA	NA
T_4	S		7.3	13	56	8	Pregnancy	31	108	nmol/L
TSH	S	29	29	24	1095	5	Lung neoplasm (not oat cell)	35	61	U/L
TPA	S	36	36	24	1095	5	Lung neoplasm (not oat cell)	35	47	U/L
TPS	S	36	36	24	1095	5	Lung neoplasm (not oat cell)	35	47	U/L
Triglycerides	S	20.9	7.7	11	56	8	Type I-DM	27	2.4	mmol/L
Triglycerides	S		15.4	17	21	8	Chronic renal failure	28	3.59	mmol/L
Triglycerides	S		17.8	128	70	3	Lipid disorders	35	1.46	mmol/L
Triglycerides	S		19.6	35	28	4	Mild hypercholesterolemia	41	1.41	mmol/L
Triglycerides	S		20.0	16	56	8	Type I-DM	27	1.88	mmol/L
Triglycerides	S		21.8	14	56	8	Hypertension	30	2.88	mmol/L
Urate	S	8.6	10.1	17	21	8	Chronic renal failure	28	477	μmol/L
Urate	S		10.3	27	56	8	Type I-DM	27	276	μmol/L
Urate	S		13.2	41	90	8	Renal post-transplantation	18	415	μmol/L
Urea	S	12.3	6.5	9	2	11	Impaired renal function	23	13.2	mmol/L
Urea	S		11.7	17	21	8	Chronic renal failure	28	21	mmol/L
Urea	S		13.0	16	56	8	Type I-DM	27	5.9	mmol/L
Urea	S		15.3	41	90	8	Renal post-transplantation	18	NA	NA
Urea	S		15.6	11	56	8	Type I-DM	27	5.26	mmol/L
Urea	S		18.3	20	4	20	Acute myocardial infarction	22	5.31	mmol/L

Abbreviations: S, serum; P, plasma; B, whole blood; U, urine; CV_I, within-subject biological variation in health; CV_I, within-subject biological variation in disease; n, number of subjects studied; NA, not available; d, period of time covered in days; s, number of samples obtained for each subject; Ref, bibliographic references; DM, diabetes mellitus.

Abbreviations for quantities: ALA, alanine aminopepotidase; ALT, alanine aminotransferase; ALP, alkaline phosphatase, Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CEA, carcinoembryonic antigen; CTx, C-telopeptide type I collagen, FT3, free triiodothyronine, FT4, free thyroxine; GGT, γ-glutamyltransferase; MCA, mucinous carcinoma-associated antigen, NAG, N-acetyl-glucosaminidase; NTx, N-telopeptide type I collagen; PBG, porphobilinogen; PAP, prostatic acid phosphatase activity; PSA, prostatic specific antigen; SCC, squamous cell carcinoma antigen; T_4, thyroxine; TPA, tissue polypeptide antigen; TPS, tissue polypeptide specific; T_3, triiodothyronine and TSH, thyroid stimulating hormone

To convert enzyme activities in μkat/L to IU/L multiply by 59.9

*Central value of the range described in the paper (mean was not reported)

†Range is given (mean value was not reported)