Serum Creatine, Creatinine, and Other Guanidino Compounds in Patients With Thyroid Dysfunction

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Serum levels of creatine (CT), creatinine (CTN), urea, guanidinosuccinic acid (GSA), guanidinoacetic acid (GAA), guanidine (G), arginine (Arg), homoarginine (Harg), argininic acid (ArgA), and α-keto-δ-guanidinovaleric acid (α-K-δ-GVA) were measured in 54 patients with hyperthyroidism, 56 with subclinical hyperthyroidism, 28 with subclinical hypothyroidism, and 51 with hypothyroidism compared with 62 euthyroid controls. In agreement with previous reports, serum CT increased (+35%) and CTN decreased (−17.6%) in hyperthyroidism as compared with normal thyroid function, whereas the opposite was seen in hypothyroidism (−17.7% and +11%, $P < .0001$). Original findings from this study are a highly significant decrease in GSA (−41.7%) and GAA (−36.8%) in hyperthyroidism and an increase in GSA (+36%) in hypothyroidism ($P < .0001$). In addition, a slight decrease in hyperthyroidism and hypothyroidism was noted for Arg (−6.2% and −13.2%, $P = .001$) and Harg (−14.8% and −18.1%, $P = .05$). By contrast, no significant change was seen in levels of urea, G, ArgA, and α-K-δ-GVA. No major differences were found for any of the compounds between subclinical hypothyroidism, euthyroidism, and subclinical hyperthyroidism. There was a highly significant positive linear correlation between urea and GSA levels in hyperthyroidism, euthyroidism, and hypothyroidism ($r = .68$, $r = .77$, and $r = .75$, $P < .0001$), taking into account that for the same increase in urea, GSA increased threefold more in hypothyroid versus hyperthyroid patients. In conclusion, apart from CT and CTN, significant changes can be found in serum levels of GSA, GAA, Arg, and Harg in patients with thyroid dysfunction. Subclinical thyroid dysfunction does not seem to induce changes in serum levels of guanidino compounds. Decreased serum GSA and GAA levels might be an additional indicator of hyperthyroidism.

THE INFLUENCE OF THYROID FUNCTION on creatine (CT), creatinine (CTN), and urea metabolism has been extensively studied. Levels of these substances are influenced by thyroid hormones by way of their action on muscle, kidney, liver, and peripheral protein metabolism.[1] In hyperthyroidism, serum CT levels increase mainly through enhanced muscle breakdown, whereas an increase of clearance and a decrease of production result in lower serum CTN levels.[2] In addition, serum urea nitrogen levels are reported to increase slightly due to an increase in peripheral protein catabolism.[2] By contrast, hypothyroidism enhances serum CTN levels due to decreased clearance and increased production of CTN.[3]

CT and CTN belong to the large group of guanidino compounds, which are molecules that contain a carbon atom surrounded by three amino functions. This class of molecules can be isolated in many different living organisms (vertebrates, invertebrates, plants, and microorganisms).[4] Guanidino compounds found in mammalia are CT, CTN, guanidinosuccinic acid (GSA), guanidinoacetic acid (GAA), arginine (Arg), homoarginine (Harg), α-keto-δ-guanidinovaleric acid (α-K-δ-GVA), argininic acid (ArgA), and guanidine (G).[5] Serum levels are disturbed in various metabolic disorders such as hyperargininemia, uremia, and cirrhosis.[6,7] The physiological role of many guanidino compounds is largely unknown. One hypothesis states that some of these compounds (CT, GSA, and G) are intermediates of the "guanidine cycle," which can be conceived of as a metabolic cycle parallel to and linked with the urea cycle, with the ability to "recycle" urea independent of N balance.[8] Other compounds like α-K-δ-GVA, ArGa, and GAA are formed from Arg and are found in increased amounts in patients with arginase deficiency. They can be synthesized by transamination and subsequent hydrogenation or transamidination, respectively.[9]

Previous studies demonstrated a positive linear correlation between serum urea nitrogen and GSA levels in various metabolic disorders such as hyperargininemia, uremia, and cirrhosis.[6,7] This was regarded as an argument in favor of the origin of GSA as an intermediate within the "guanidine cycle." This metabolic cycle is thought to ensure the production of CT despite aberrations in nitrogen balance. Since these aberrations occur frequently in thyroid dysfunction, the present study was made with the purpose of confirming the previously presumed metabolic relationship between urea and GSA. In addition, we wanted to systematically determine serum levels of all other guanidino compounds in both hyperthyroidism and hypothyroidism.

For measuring serum levels of guanidino compounds, an amino acid analyzer was used. We used chromatography by means of a cation-exchange column for separation of guanidino compounds.[9] Detection was possible using the fluorescence ninhydrin method.[10]

Serum levels of CT, CTN, urea, GSA, GAA, Arg, Harg, α-K-δ-GVA, ArgA, and G were determined for the different modes of thyroid dysfunction. We considered the potential use of these values as additional parameters of thyroid function. Furthermore, as for uremia and cirrhosis, we wanted to confirm a linear correlation between serum urea nitrogen and GSA levels in thyroid disease.[6,7]

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SUBJECTS AND METHODS

Patients

At two separate thyroid disease consultations, guanidino compound levels were measured in 251 patients (51 men and 200 women) with different degrees of thyroid dysfunction. Patients aged 15 to 93 years were separated into five groups according to thyroid function: 51 patients were diagnosed with hypothyroidism (FT_3 ↓, FT_4 ↓, and TSH ↑; mean age, 58.5 ± 18.9 years); 28 with subclinical hypothyroidism (FT_3 normal [nl], FT_4 nl, and TSH ↑; 62.0 ± 16.0 years); 62 with euthyroidism (FT_3 nl, FT_4 nl, and TSH nl; 52.0 ± 17.2 years); 56 with subclinical hyperthyroidism (FT_3 nl, FT_4 nl, and TSH ↓; 58.4 ± 13.5 years); and 54 with hyperthyroidism (FT_3 ↑, FT_4 ↑, and TSH ↓; 52.3 ± 18.4 years). The classification was enforced regardless of etiology or imposed therapy. The distribution of patients can be regarded as representative of a normal population presenting for thyroid disease consultation.

Collection and Preparation of Samples

Sampling was usually performed at the first consultation with a patient. After clotting, the blood was centrifuged at 2,200 × *g* at 6°C for 10 minutes. A portion of the serum was reserved for urea determination. The remaining serum was stored at −75°C until analyzed. For determination of the guanidino compounds, samples were deproteinized by mixing equal volumes of a 200-g/L trichloroacetic acid solution with serum. The proteins were centrifuged in a Beckman microfuge (Beckman Instruments International, Geneva, Switzerland). Two hundred microliters of supernatant was used for analysis.

Measurement of TSH, FT_3, and FT_4

For determination of FT_3, FT_4, and TSH, different radioimmunoassays were used. FT_3 level was measured using the Amerlex-MAB FT_3 kit (Johnson & Johnson, Amersham, UK; nl, 3.4 to 7.2 pmol/L). For assaying FT_4, the Amerlex-MAB FT_4 kit (Johnson & Johnson; nl, 11 to 24 pmol/L) was used. TSH was assayed with the RIA-gnost TSH kit (CIS Bio International, Gif-Sur-Yvette, France; nl, 0.25 to 4 μIU/mL).

Measurement of Guanidino Compounds and Urea

The concentration of guanidino compounds was determined using a Biotronik LC 5001 (Biotronik, Maintal, Germany) amino acid analyzer adapted for guanidino compound determination. The guanidino compounds were separated over a cation-exchange column using sodium citrate buffers and were detected by the fluorescence ninhydrin method as reported in detail.[9] Serum urea nitrogen was determined with diacetylmonoxime as described by Ceriotti.[11]

Standard guanidino compounds were acquired from Sigma Chemical (St Louis, MO), and CT and CTN were from Merck (Darmstadt, Germany). α-K-δ-GVA was synthesized enzymatically as described previously.[5] All other reagents were obtained from Merck and were of analytical grade.

Statistics

Guanidino compound levels are given as the mean ± SE for guanidino compounds present at detectable levels. If, in addition to detectable levels of a particular guanidino compound, no levels could be detected in some samples, then the results are given as a range from less than the detection limit to the highest level obtained in this group. Results were compared using ANOVA with post hoc comparison (ANOVA, Fisher's PLSD, and Scheffe test). The interrelationships of individual serum GSA levels with the corresponding serum urea, CTN, and G levels were assessed by linear correlation studies in which the partial correlation coefficient is considered in order to correct for confounding influences by correlations between other variables. Significance was determined at P less than .01, to avoid spurious significance levels because of repeated testing (Bonferroni method).

RESULTS

Serum CT levels increase as thyroid function increases (ANOVA, $P < .0001$). An increase in CT levels is found from hypothyroidism (38.2 ± 4.4 μmol/L, −17.7%) to hyperthyroidism (62.7 ± 27.8 μmol/L, +35%). The level of significance between serum levels in hyperthyroidism and euthyroidism (46.4 ± 3.1 μmol/L) is .001 (Fisher's post hoc analysis) (Table 1).

Serum CTN levels decrease with increasing thyroid function ($P < .0001$). There is a decrease in CTN levels from hypothyroidism (90.1 ± 3.5 μmol/L, +11%) to hyperthyroidism (66.8 ± 2.5 μmol/L, −17.6%). The level of significance between serum levels in hyperthyroidism and euthyroidism (81.1 ± 2.4 μmol/L) is .0002 and in hypothyroidism and euthyroidism .02.

There is no significant change in serum urea nitrogen levels. Urea nitrogen levels in hypothyroidism and hyperthyroidism are comparable to those in euthyroidism (5.45 ± 0.20 mmol/L).

There is an increase in the ratio CT/CTN as thyroid function increases ($P < .0001$). The ratio increases from hypothyroidism (0.45 ± 0.05, −26.2%) to hyperthyroidism (0.98 ± 0.06, +61%). The level of significance between the ratios in hyperthyroidism and euthyroidism (0.61 ± 0.04) is .0001 and in hypothyroidism and euthyroidism .02.

There is an increase in the ratio urea/CTN with increasing

Table 1. Serum Levels of CT, Urea, GSA, GAA, G, Arg, Harg, ArgA and GVA (mean ± SD), Percent Change of Normal (euthyroid) Values, and Level of Significance (Fisher's post hoc analysis) for 51 Patients With Hypothyroidism, 28 With Subclinical Hypothyroidism, 62 With Euthyroidism, 56 With Subclinical Hyperthyroidism, and 54 With Hyperthyroidism

	Hypothyroidism (n = 51)			Subclinical Hypothyroidism (n = 28)			Euthyroidism (n = 62)	Subclinical Hyperthyroidism (n = 56)			Hyperthyroidism (n = 54)		
	Mean ± SD	% Change	*P*	Mean ± SD	% Change	*P*	Mean ± SD	Mean ± SD	% Change	*P*	Mean ± SD	% Change	*P*
CT (μmol/L)	38.2 ± 4.4	−17.7	NS	45.1 ± 5.0	−2.8	NS	46.4 ± 3.1	44.5 ± 3.2	−4.1	NS	62.7 ± 27.8	+35	.001
CTN (μmol/L)	90.1 ± 3.5	+11	.018	83.9 ± 3.2	+3	NS	81.1 ± 2.4	82.6 ± 2.7	+2	NS	66.8 ± 2.5	−17.6	.0002
Urea (mmol/L)	6.03 ± 0.37	+11	NS	5.67 ± 0.48	+4	NS	5.45 ± 0.20	5.65 ± 0.27	+4	NS	5.76 ± 0.27	+6	NS
CT/CTN	0.45 ± 0.05	−26.2	.025	0.56 ± 0.06	−8.2	NS	0.61 ± 0.04	0.58 ± 0.05	−4.9	NS	0.98 ± 0.06	+61	<.0001
Urea/CTN	0.067 ± 0.003	−1.5	NS	0.067 ± 0.005	−1.5	NS	0.068 ± 0.002	0.070 ± 0.003	+3	NS	0.088 ± 0.004	+29	<.0001
GSA (μmol/L)	0.49 ± 0.06	+36	.005	0.36 ± 0.04	0	NS	0.36 ± 0.03	0.36 ± 0.03	0	NS	0.21 ± 0.02	−41.7	.001
GAA (μmol/L)	2.32 ± 0.12	+2	NS	1.73 ± 0.13	−24.1	.0005	2.28 ± 0.09	1.90 ± 0.08	−16.7	.003	1.44 ± 0.07	−36.8	<.0001
G (μmol/L)	0.28 ± 0.05	+22	NS	0.24 ± 0.03	+4	NS	0.23 ± 0.02	0.27 ± 0.02	+17	NS	0.21 ± 0.02	−8.7	NS
Arg (μmol/L)	125 ± 4	−13.2	.0007	121 ± 5	−16	.001	144 ± 4	128 ± 4	−11.1	.003	135 ± 5	−6.2	NS
Harg (μmol/L)	1.49 ± 0.09	−18.1	.008	1.56 ± 0.14	−14.3	NS	1.82 ± 0.09	1.52 ± 0.08	−16.5	.014	1.55 ± 0.09	−14.8	.029
ArgA (μmol/L)	0.088 ± 0.007	−10.2	NS	0.082 ± 0.010	−16.3	NS	0.098 ± 0.007	0.073 ± 0.009	−25.5	.019	0.082 ± 0.008	−16.3	NS
GVA (μmol/L)	0.134 ± 0.014	−8.2	NS	0.122 ± 0.011	−16.4	NS	0.146 ± 0.007	0.150 ± 0.009	+3	NS	0.160 ± 0.009	+10	NS

thyroid function ($P < .0001$). The ratio increases from hypothyroidism (0.067 ± 0.003, -1.5%) to hyperthyroidism (0.088 ± 0.004, $+29\%$). The level of significance between the ratios in hyperthyroidism and euthyroidism (0.068 ± 0.002) amounts to .0001.

Serum GSA levels decrease as thyroid function increases ($P < .0001$). There is a decrease in GSA levels from hypothyroidism (0.49 ± 0.06 μmol/L, $+36\%$) to hyperthyroidism (0.21 ± 0.02 μmol/L, -41.7%). The level of significance between serum levels in hyperthyroidism and euthyroidism (0.36 ± 0.03 μmol/L) is .001 and in hypothyroidism and euthyroidism .005.

Serum GAA levels decrease with increasing thyroid function ($P < .0001$). A decrease in GAA levels is found from hypothyroidism (2.32 ± 0.12 μmol/L, $+2\%$) to hyperthyroidism (1.44 ± 0.07 μmol/L, -36.8%). The level of significance between serum levels in hyperthyroidism and euthyroidism (2.28 ± 0.09 μmol/L) is .0001, in subclinical hyperthyroidism and euthyroidism .003, and in subclinical hypothyroidism and euthyroidism .0005.

For G, there is a tendency for serum levels to decrease as thyroid function increases. However, this is not significant. G levels slightly decrease from hypothyroidism (0.28 ± 0.05 μmol/L, $+22\%$) to hyperthyroidism (0.21 ± 0.02 μmol/L, -8.7%).

For Arg, there is a slight decrease in serum levels in both directions of thyroid dysfunction ($P = .001$). A decrease in Arg levels is found from euthyroidism (144 ± 4 μmol/L) to hyperthyroidism (135 ± 5 μmol/L, -6.2%) and hypothyroidism (125 ± 4 μmol/L, -13.2%). The level of significance between serum levels in subclinical hyperthyroidism and euthyroidism is .003, in subclinical hypothyroidism and euthyroidism .001, and in hypothyroidism and euthyroidism .0007.

For Harg, there is also a slight decrease in serum levels in both directions of thyroid dysfunction ($P = .05$). Harg levels decrease from euthyroidism (1.82 ± 0.09 μmol/L) to hyperthyroidism (1.55 ± 0.09 μmol/L, -14.8%) and hypothyroidism (1.49 ± 0.09 μmol/L, -18.1%). The level of significance between serum levels in hyperthyroidism and euthyroidism is .029, in subclinical hyperthyroidism and euthyroidism .014, and in hypothyroidism and euthyroidism .008.

Finally, for ArgA, there is a tendency for serum levels to change in the same way. However, this is not significant. There is a slight decrease in ArgA levels from euthyroidism (0.098 ± 0.007 μmol/L) to hyperthyroidism (0.082 ± 0.008 μmol/L, -16.3%) and hypothyroidism (0.088 ± 0.007 μmol/L, -10.2%).

There is no significant change in serum α-K-δ-GVA levels. α-K-δ-GVA levels in hypothyroidism and hyperthyroidism are comparable to those in euthyroidism (0.146 ± 0.007 μmol/L).

No detectable serum levels could be found for α-*N*-acetylarginine, β-guanidinopropionic acid, γ-guanidinobutyric acid, and methylarginine for any of the groups of thyroid disease patients.

One of the closest correlations between all guanidino compounds was found between serum urea nitrogen and GSA levels in patients with hyperthyroidism, euthyroidism, and hypothyroidism ($r = .68$, $r = .77$, and $r = .75$, respectively, $r = .63$ overall, $P < .0001$; Fig 1). However, the slope of the linear function curve is almost threefold sharper in hypothyroidism compared with hyperthyroid patients. As expected, a similar close correlation was found between serum urea nitrogen and CTN levels for the different levels of thyroid function ($r = .57$, $r = .50$, and $r = .69$, respectively, $r = .51$ overall, $P < .0001$).

As in any population, serum urea nitrogen levels increase with age ($r = .440$, $P < .0001$), a phenomenon that can be attributed to decreasing renal function. There are no significant differences in the distribution of age (and sex) between the different patient groups. As a result, age can be largely dismissed as a mediating factor for the (lack of) change in serum urea nitrogen levels with thyroid function.

DISCUSSION

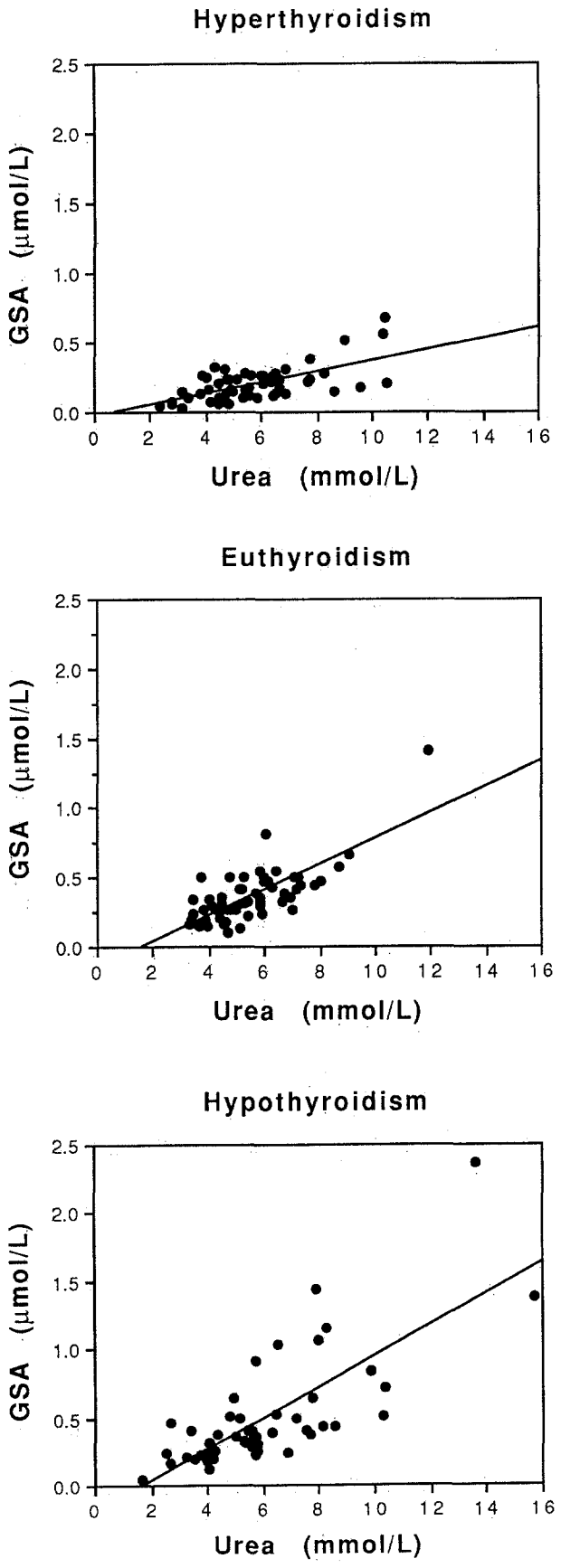
This study is interesting because a series of guanidino compounds were accurately measured in serum in a large group of patients with different levels of thyroid dysfunction. We were able to confirm the changes in serum CT and CTN levels dependent on thyroid function that have been reported.[1]

In 1957, Kuhlback[12] presented the first systematic survey of serum CT and CTN levels in patients with thyroid dysfunction. He used the Jaffe-Folin picrate color reaction with photoelectric colorimetry before and after heating a deproteinized plasma filtrate. In this way, he was able to determine serum CT levels in hyperthyroidism (n = 40) at 1.63 mg/dL (124 μmol/L), in euthyroidism (n = 37) at 0.691 mg/dL (52.7 μmol/L), and in hypothyroidism (n = 8) at 1.02 mg/dL (77.8 μmol/L). For these three groups, serum CTN levels were determined at, respectively, 0.639 mg/dL (56.5 μmol/L), 0.869 mg/dL (76.8 μmol/L), and 1.28 mg/dL (113 μmol/L). Almost all differences between serum levels for the three groups appeared to be significant ($P = .001$). These changes in serum levels dependent on thyroid function have been confirmed in other studies.[2,13] They are now being confirmed by our own results. By means of column chromatography and a fluorometric detection method, we found the same range of difference with even higher significance.

Especially in hyperthyroidism, these changes are apparent. Serum CT levels increase mainly through muscle breakdown, with an increase of CT released and a decrease of newly synthesized CT taken up by muscles.[12,14] A decrease of serum CTN levels is explained by a higher CTN clearance as a result of increased glomerular filtration rate (GFR) together with an increase in cardiac output or an increase in proximal tubular sodium reabsorption (proximal tubular hypertrophy) through tubuloglomerular feedback.[1,2,13] In addition, a higher CTN clearance could also be due to increased tubular secretion.[15] CTN production is lower as a result of decreased muscle mass and a disturbed transformation of CT into CTN due to muscle breakdown.[13,15]

As previously reported, hypothyroidism is marked by an increase in serum CTN levels. This results from a lower CTN clearance with decreased GFR and higher CTN production due to an immediate release of CTN through muscle breakdown (rhabdomyolysis).[1,3]

A limited increase in serum urea nitrogen levels with increasing thyroid function is reported. One report mentions serum urea nitrogen levels, determined by means of an autoanalyzer, of about 14.3 mg/dL (5.11 mmol/L) for hyperthyroidism



(n = 118), 12.0 mg/dL (4.28 mmol/L) for euthyroidism (n = 176), and 13.8 mg/dL (4.93 mmol/L) for hypothyroidism (n = 14).[13] In another report, no significant change in serum levels with increasing thyroid function is found.[2] We were able to confirm this last finding.

In some studies, an increased peripheral protein catabolism in hyperthyroidism is supposed to be only partly counterbalanced by an increased GFR and a decreased tubular urea reabsorption.[13,15] Results from our study suggest that there is no net effect of hyperthyroidism on serum urea, which could be explained by a complete counterbalance of increased urea production and clearance. The latter is normally regarded to be dependent to a greater extent on age than on thyroid function. In this study, we furthermore demonstrated an equal distribution of age among the different levels of thyroid function.

No significant differences were found between "subclinical" thyroid dysfunction and euthyroidism. Since the thyroid function states of subclinical hyperthyroidism (FT_3 nl, FT_4 nl, and TSH ↓) and subclinical hypothyroidism (FT_3 nl, FT_4 nl, and TSH ↑) are clinically less important, they do not entail major biochemical repercussions.

Before the availability of direct measurement of T_3, T_4, and TSH, the ratio CT/CTN was regarded as a sensitive indicator of hyperthyroidism apart from basal metabolic rate and serum cholesterol level.[12] More recently, attention has been drawn to the ratio urea/CTN.[13,15] This study confirms that an increase in the two ratios can designate hyperthyroidism, although large overlaps exist between groups. These tests might still be useful in patients in whom measurement of T_3, T_4, and TSH is unreliable, eg, patients with thyroid hormone resistance (when comparing groups and not individual patients).

In this study, we showed for the first time that serum levels of GSA also change with thyroid function. These changes are more significant than changes in CT or CTN. An increase in GSA levels in hypothyroidism might be the result of decreased renal function. Previously, it has been stated that serum GSA levels are useful as an indicator of incipient renal insufficiency or as a parameter for residual functional liver mass.[6,7] This study shows that serum GSA levels might also be of some value in measuring thyroid hormone influence at the cellular level, although large overlaps exist with normal values.

One of the most striking correlations between guanidino compounds was found between serum urea nitrogen and GSA levels for the whole range of thyroid function (r = .63). The same association has been found in patients with uremia and cirrhosis (child B and C) with an even higher correlation coefficient (r = .82 and r = .85, respectively).[6,7] One possible explanation for this metabolic relationship might be the hypothesis that GSA is an intermediate within the "guanidine cycle." This cycle has been conceived as a hypothetical metabolic cycle parallel to and linked with the urea cycle. Its purpose would be to "recycle" urea to ensure the production of CT independently of N balance.[8] The positive linear correlations between serum

Fig 1. Positive linear correlation between serum urea nitrogen levels of patients with different types of thyroid dysfunction and the corresponding serum GSA levels. The slope of the linear function curve decreases as thyroid function increases.

urea nitrogen and GSA levels in various metabolic disorders (eg, uremia, cirrhosis, and, at this point, also thyroid dysfunction) are only a weak argument in favor of a metabolic relationship and should actually be confirmed by direct experimental procedures.

A linear correlation between serum urea nitrogen and GSA levels can be maintained throughout the whole range of thyroid function, despite the fact that serum urea nitrogen levels are not directly affected by thyroid dysfunction, because of the decrease in the slope of the linear function curves as thyroid function increases. Similarly, a close correlation can be found between serum urea nitrogen and CTN levels, although the correlation coefficients are generally lower for the different levels of thyroid function ($r = .51$ overall, with the exception of hypothyroidism).

For GAA also, there is a decrease in serum levels with increasing thyroid function. This decrease is only significant in overt hyperthyroidism, as opposed to a decrease in GSA for the whole range of thyroid function. With reference to GSA and GAA, there is only a tendency for serum G levels to decrease as thyroid function increases. There is a slight decrease in serum Arg and Harg levels in both directions of thyroid dysfunction. For serum ArgA levels, a similar tendency can be observed. These changes are not easily accounted for, and further studies will be necessary to elucidate the influence of thyroid function on these metabolic pathways.

In conclusion, serum CT and CTN levels are influenced by thyroid function, as shown previously. There is a highly significant decrease in serum GSA and GAA levels as thyroid function increases and a slight decrease in Arg and Harg levels in both directions of thyroid dysfunction. The most significant changes in serum guanidino compounds are found in hyperthyroidism. There are no major differences in serum levels between subclinical hypothyroidism, euthyroidism, and subclinical hyperthyroidism. Although serum urea nitrogen levels do not change significantly on their own, there is a significant positive linear correlation between serum urea nitrogen and GSA levels for the different modes of thyroid dysfunction.

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