American Journal of Gastroenterology
© 2005 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2005.00268.x

Biochemical Assessment of Niacin Deficiency Among Carcinoid Cancer Patients

Girish M. Shah, Ph.D.,[1] Rashmi G. Shah, M.Sc.,[1] Helene Veillette, M.D.,[1] James B. Kirkland, Ph.D.,[2] Janice L. Pasieka, M.D.,[3] and Richard R. P. Warner, M.D.[4,5]

[1]*Laboratory for Skin Cancer Research, CHUL Research Center (CHUQ), Faculty of Medicine, Laval University, Sainte-Foy, Quebec, Canada;* [2]*Department of Human Biology and Nutritional Sciences, University of Guelph, Guelph, Ontario, Canada;* [3]*Tom Baker Cancer Center and Foothills Medical Center, University of Calgary, Calgary, Alberta, Canada;* [4]*Carcinoid Cancer Foundation, Inc., White Plains, New York; and* [5]*Division of Gastroenterology, Mount Sinai School of Medicine, New York, New York*

OBJECTIVE: Carcinoid cancer patients often have elevated levels of serotonin or its precursor 5-hydroxytryptophan. Normally, serotonin synthesis accounts for a small fraction of tryptophan catabolism, which should be directed along a pathway that allows partial conversion to niacin; hence, increased diversion of tryptophan toward serotonin could cause variable degrees of niacin deficiency in carcinoid patients. Therefore, the prevalence of niacin deficiency among carcinoid patients was investigated by clinical assessment of pellagra and biochemical assessment of whole blood niacin number, a ratio derived from two biologically active forms of niacin (NAD/NADP $\times$ 100).

METHODS: Clinical and biochemical niacin status were assessed in a cohort of newly diagnosed carcinoid patients with carcinoid syndrome (CCS, n = 36), carcinoid patients without carcinoid syndrome (CWCS, n = 32) and noncarcinoid controls (n = 24) recruited at two primary care clinics. Other aspects of serotonin metabolism were measured by analyses of plasma serotonin and tryptophan and urinary excretion of 5-hydroxyindoleacetic acid.

RESULTS: Biochemical niacin deficiency (niacin number $<$ 130) was significantly more common in CCS patients (10 out of 36) compared to controls ($p < 0.05$, Fisher's exact test), while CWCS patients displayed an incidence that was not significantly elevated (4 out of 32). Only one CCS patient, who was also identified biochemically as niacin deficient, was clinically diagnosed with pellagra.

CONCLUSION: Biochemical niacin deficiency is more prevalent among newly diagnosed CCS patients than in controls. Manifestation of pellagra is a less sensitive indicator, and dependence on this endpoint could lead to a lack of appropriate nutritional support for this group of patients.

(Am J Gastroenterol 2005;100:2307–2314)

INTRODUCTION

Carcinoids are rare tumors derived predominantly from enterochromaffin cells of the diffuse neuroendocrine system, most frequently observed in the gastrointestinal tract and bronchopulmonary system (1–3). Many carcinoids can produce a variety of bioactive amines and peptides, including serotonin, chromogranins, bradykinin, histamine, neuron-specific enolase, calcitonin, pancreatic polypeptide, and prostaglandins. One of the most common and best characterized of these substances is serotonin that is derived from amino acid tryptophan via intermediate synthesis of 5-hydroxytryptophan (5-HTP) (Fig. 1). Serotonin is further metabolized by monoamine oxidase in the periphery to 5-hydroxyindoleacetic acid (5-HIAA) that is excreted in the urine (4, 5).

A subset of carcinoid patients suffer from an advanced form of the disease called carcinoid syndrome that is characterized by symptoms such as flushing, recurrent diarrhea, abdominal cramps, skin abnormalities, asthmatic wheezing, and valvular heart diseases. These symptoms are largely associated with elevated levels of serotonin in systemic circulation and increased urinary excretion of 5-HIAA. Some of the carcinoid patients also suffer from a non-classical form of carcinoid syndrome, which is accompanied by release of the serotonin precursor 5-HTP, which is converted to serotonin in the kidney. Apart from these patients, nearly 25% of the asymptomatic carcinoid patients also have elevated levels of serotonin (2, 4–7). Thus, a significant proportion of carcinoid patients divert excess tryptophan toward the serotonin/5-HTP pathway that could reduce availability of this amino acid for other metabolic purposes.

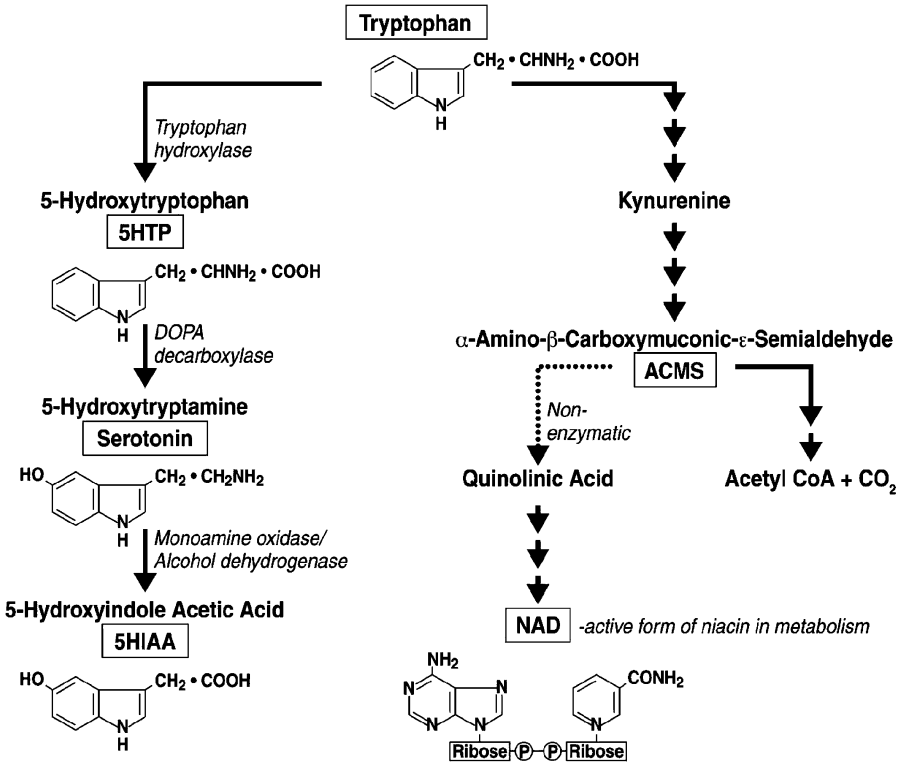

Figure 1. Competing pathways of tryptophan catabolism. Tryptophan is degraded by two competing pathways for formation of either serotonin or ACMS, which is a precursor of NAD, an active form of niacin in metabolism. Serotonin is further metabolized to 5-HIAA which is excreted in urine. The excessive production of serotonin by carcinoid tumor can cause reduced availability of tryptophan for NAD formation.

Apart from its requirement in synthesis of proteins, tryptophan is catabolically degraded by two competing pathways that produce either serotonin or α-amino-β-carboxymuconic-ε-semialdehyde (ACMS) (Fig. 1). ACMS is then degraded, or processed through quinolinate to form β-nicotinamide adenine dinucleotide (NAD), which is an active form of niacin (vitamin B3) in metabolism (8). In healthy persons, only 1% of tryptophan is catabolized to form serotonin, whereas the rest is catabolized via kynurenine pathway toward ACMS (9). ACMS has to accumulate, allowing a spontaneous chemical conversion to quinolinate, to support niacin status (8). If the flow through ACMS is limited, the formation of NAD from tryptophan will be extremely low. In carcinoid syndrome patients, up to 99% of tryptophan can be catabolized to serotonin (10), which will significantly reduce the flow through ACMS. Indeed, pellagra, the clinical condition caused by severe niacin deficiency, characterized by the 3Ds—dermatitis, diarrhea, and dementia, has been reported in some carcinoid patients (10–14). Despite these reports, niacin deficiency is not often appreciated in carcinoid patients, possibly because pellagra symptoms are similar to symptoms of the carcinoid syndrome and a reliable biochemical marker for niacin status has not been established for these patients. Additionally, many carcinoid patients with less aggressive synthesis of serotonin would have reduced (2–90%) diversion of tryptophan toward serotonin pathway (6, 10); and these patients could suffer from sub-clinical niacin deficiency without displaying any signs of pellagra. Hence, there is a need to examine their niacin status by another method.

In clinical practice, niacin status of a patient may be evaluated by urinary excretion of niacin and its metabolites that are assayed by fluorometric or bacteriological methods (8). More recently, human niacin status is determined by a sensitive biochemical assay called niacin number that is derived from the whole blood concentrations of two of the biologically active forms of niacin, namely NAD and NADP (8, 15–17). Between these two forms, it is NAD levels that respond to the niacin status of the individual, *i.e.*, they are significantly lowered during niacin deficiency and they increase rapidly after niacin supplementation. In contrast, NADP levels remain reasonably constant under different conditions of niacin status. Hence, niacin number (NAD/NADP $\times$ 100) (15, 16) provides a sensitive measure of niacin status. In various studies described above, healthy individuals with good niacin intake have niacin numbers above 130 (8, 15–17), and upon intake of niacin-deficient diet for 3 wks, their niacin number drops below 130 (16). Hence, lowering of niacin number below 130 is an accepted index of niacin deficiency.

Here, we report the extent of clinical and biochemical niacin deficiency observed in a cohort of 68 carcinoid cancer patients with or without carcinoid syndrome and 24 non-carcinoid controls. We also compare it with three other parameters that reflect serotonin metabolism, namely plasma serotonin and tryptophan, and urinary 5-HIAA.

Table 1. Clinical Characteristics of the Three Study Groups: Carcinoid Patients with Carcinoid Syndrome (CCS), Carcinoid Patients Without Carcinoid Syndrome (CWCS), and Noncarcinoid Control (CON)

Characteristics	CCS	CWCS	CON
Number of subjects	36	32	24
Median age in years (range)	58 (25–80)	59 (22–75)	42 (23–72)
Males/Females	18/18	8/24	10/14
Primary carcinoid tumor type (number of cases)			
Foregut	4	9	
Midgut	24	18	
Hindgut	1	3	
Other or unknown sites	7	2	
Site of carcinoid-metastasis (number of cases)			
Liver	27	13	
Intestinal regional	4	6	
Other organs	4	10	
Nonmetastatic	1	3	
Composition of control group (number of cases)			
(a) Other neuroendocrine tumors (VIPoma, pancreatic cancers, pheochromocytoma)			5
(b) Other cancers (thyroid, intestine)			2
(c) Gastrointestinal diseases (malabsorption, diarrhea, cholecystitis)			4
(d) Nongastrointestinal diseases (dermatitis, flushing, schizophrenia)			3
(e) Healthy volunteers			10

METHODS

Subjects

Newly diagnosed carcinoid cancer patients, and noncarcinoid controls, were recruited at the Carcinoid Cancer Clinic of New York, NY, USA (RRPW) and at the Tom Baker Cancer Center and Foothills Medical Center of University of Calgary, Calgary, Alberta, Canada (JLP) (Table 1). Consent had been obtained from each patient after full explanation of the purpose and nature of all procedures used. The investigation was approved by the ethical committees and the Institutional Review Boards of Mount Sinai School of Medicine of New York and the University of Calgary. The biochemical analyses were approved by the Committee of Ethics in Clinical Research at Laval University. Among the 92 subjects of this study, there were 77 Caucasians, 6 Hispanics, 5 African Americans, and 4 Asians. Samples for biochemical analyses were withdrawn prior to the start of treatment regimes, and patients who were being treated with somatostatin analogs were excluded from the study.

The carcinoid patients were divided into those with carcinoid syndrome (CCS group, n = 36) and those without carcinoid syndrome (CWCS, n = 32) (Table 1). CCS patients had confirmed tissue diagnosis of carcinoid, laboratory proof of excessive serotonin production (as evidenced by abnormally increased levels of blood serotonin and urinary excretion of 5-HIAA), and one or more of the following three clinical manifestations: facial flushing, diarrhea, and bronchospasm (wheezing). All the patients with mild as well as severe symptoms of carcinoid syndrome were included in the CCS group. CWCS patients were those with confirmed tissue diagnosis of carcinoid, but were free of any of the three major symptoms of carcinoid syndrome. The noncarcinoid control group (CON, n = 24) was composed of individuals suffering from noncarcinoid endocrine diseases, other cancers, gastrointestinal and nongastrointestinal diseases, as well as healthy subjects chosen from among the volunteers and relatives of the patients (Table 1). The inclusion of other patients suffering from symptoms resembling carcinoid syndrome in the control group allowed us to discriminate between the influences of symptoms alone from the carcinoid-associated derangement of serotonin metabolism.

Collection of Blood, Plasma, and Urine

Fasting venous blood samples were collected in Vacutainer tubes containing heparin (for whole blood) or citrate (for plasma). Plasma was obtained by centrifugation of citrate-treated blood at 120 × *g* for 30 min at 4°C. Plasma and whole blood were dispensed in 1 mL aliquots in cryotubes, frozen in dry ice and stored at −80°C until shipping in dry ice to Laval University for the biochemical analyses on coded samples. The 24-h urine samples were stored in acidified condition at 4°C, and analyzed in the clinical laboratories at each of the participating centers. The biochemical data were pooled with the clinical observations prior to statistical analyses.

Biochemical Analyses

NIACIN NUMBER. To determine niacin number (NAD/NADP × 100) (15), two 1 mL aliquots of each whole blood sample were dissolved in alkali followed by acid extraction (18). During the first stage of extraction, the reduced forms of the nucleotides become oxidized, and in the second stage, the oxidized forms (NAD^+ and $NADP^+$) are stably extracted by acid, making this assay a measurement of total NAD and NADP pools. NAD and NADP in the acid extracts were determined by cycling assays using alcohol dehydrogenase and isocitrate dehydrogenase, respectively (15, 18). For each extract, two concentrations were assayed in triplicate in the microplates containing a series of standard NAD or NADP

(0–20 pmol per well). For each batch of analyses, extraction efficiencies were determined by inclusion of an NAD or NADP-spiked blood sample of the same control subject. Data were obtained with a μQuant plate reader and analyzed by KC4 v3.0 software (BioTeK Instruments).

PLASMA TRYPTOPHAN AND SEROTONIN. Plasma serotonin and tryptophan were analyzed at the clinical laboratory of the Genetics Service of the Fleurimont Hospital of University of Sherbrooke, Canada, utilizing standard C_{18} reversed phase HPLC column (APCI) followed by mass spectroscopy in 110 LC/MSD from Agilent Technology (19).

URINARY 5-HIAA. Analysis of 5-HIAA was carried out by clinical laboratories of each of the participating centers on acidified urine samples utilizing standard HPLC technique followed by electrochemical detection (20).

Statistical Analyses

The statistical analyses were performed using Splus 6.0 Professional release 1 (Insightful Corp, Seattle, WA, USA) (21). Data were presented as a box plot where the box represents the middle two quartiles in which mean (X) and median (line) values are marked and the highest and the lowest quartiles extend from the box. The minimum, mean, and maximum values of reference populations from the literature were marked for each parameter. The significance of differences of means was derived from nonparametric Wilcoxon rank sum test, since these groups did not have a normal distribution of data that could be subjected to a standard two sample *t*-test. We also analyzed the proportion of patients that exceeded cut-offs for serotonin, 5-HIAA, tryptophan, and niacin number by the 2-tailed Fisher's exact test, a nonparametric test optimized for determining the incidence of an event in smaller sample sizes. For both analyses, p values of less than 0.05 (denoted by a $*$) were considered significantly different from the control group.

RESULTS

Increase in Plasma Serotonin and Urinary 5-HIAA in the CCS Patients

Plasma serotonin levels in reference adult populations range from 0.03 to 0.07 μM, with an average of 0.04 μM (22). In our control group, serotonin levels were 0.05 ± 0.01 μM (mean $\pm$ SE, n $=$ 24, range: $<$0.02–0.22 μM) (Fig. 2A). Relative to controls, average serotonin levels were elevated by 16-fold in the CCS group (0.78 ± 0.14 μM, n $=$ 36, 0.04–3.2, $p = 0^*$) and by about threefold in the CWCS group (0.16 ± 0.03 μM, n $=$ 32, 0.02–0.6, $p = 0.0039^*$). Using a cut-off value of 0.07 μM, the highest serotonin concentration in control population, it was evident that 83% (30/36) of the CCS patients and 53% (17/32) of the CWCS patients had higher than normal levels of serotonin. Thus, both the carcinoid groups had a significant increase in incidence of elevated serotonin levels ($p < 0.001^*$, Fisher's exact test).

The increases in plasma serotonin levels were correlated with changes in urinary excretion of 5-HIAA (Fig. 2B). The

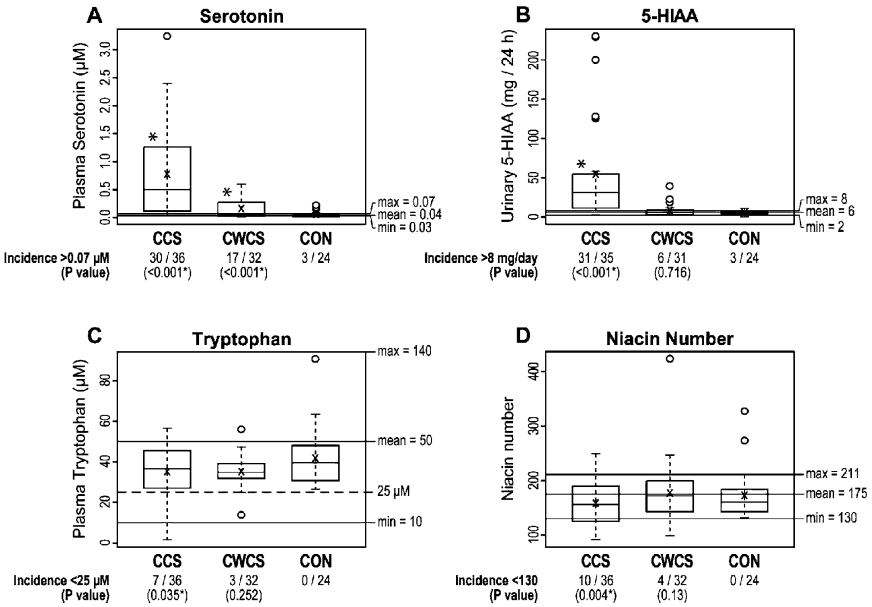

Figure 2. Biochemical analyses of serotonin-related parameters in carcinoid patients. Patients were divided in three groups: carcinoid patients with carcinoid syndrome (CCS), carcinoid patients without carcinoid syndrome (CWCS), and noncarcinoid controls (CON). Various samples from these patients were analyzed for (*A*) plasma serotonin, (*B*) urinary 5-HIAA, (*C*) plasma tryptophan, and (*D*) whole blood niacin number. The data are represented as the box plot. For tryptophan (Fig. 2C), an additional line is drawn at 25 μM, which is the lowest value observed in controls. The * above the box signifies statistically significant difference of mean values between the given group and the controls, as determined by nonparametric Wilcoxon rank sum test ($p < 0.05$). The data were also subjected to Fisher's exact test to determine statistical significance of the incidence of values which fell well above or below the control values, as described in the text.

24-h urinary 5-HIAA in adult reference populations has a range of 2–8 mg per day with an average value of 6 mg per day. The average 5-HIAA excretion in our control group was 5.3 ± 0.9 mg per day (mean ± SE, n = 24, range: 1.9–11.0), which increased 10-fold in the CCS group (54.4 ± 13.0, n = 35, 2.4–230, $p = 0.0001^*$), but only marginally in the CWCS group (8.0 ± 1.7, n = 31, 2.2–11.5, $p = 0.568$). Compared to controls (3/24 above 8 mg per day), the incidence of elevated urinary 5-HIAA was greater in the CCS group (31/35 above 8 mg per day, $p < 0.001$,* Fisher's exact test), but not in the CWCS group (6/31 above 8 mg per day, $p = 0.716$).

Increased Incidence of Low Tryptophan Levels in the CCS Patients

The average plasma tryptophan of the control group was 41.7 ± 2.6 (mean ± SE, n = 24, range: 26.7–90.6), which tended to decrease in the CCS (35.2 ± 2.4, n = 36, 1.5–56.5, $p = 0.172$) and CWCS (35.1 ± 1.4, n = 32, 13.7–55.9, $p = 0.0911$) groups (Fig. 2C). Although the mean values for CCS and CWCS were not statistically different from controls, the Fisher's exact test revealed that the incidence of patients with low tryptophan values was significantly elevated in CCS group. The occurrence of very low tryptophan values (<25 μM) was observed in 7/36 CCS patients ($p = 0.035^*$) and 3/32 CWCS patients ($p = 0.252$). In fact, two of the CCS patients had tryptophan values even below 10 μM (1.5 and 8.3 μM). Thus, the incidence of very low tryptophan levels was significantly increased in the CCS patients.

Increased Incidence of Niacin Deficiency in the CCS Patients

Only 1 patient, belonging to the CCS group, who had a primary carcinoid tumor at an unknown site and metastasis in liver, was diagnosed as clinically malnourished with signs of pellagra, including diarrhea and sun-sensitive skin lesions. Interestingly, this patient had high serotonin (0.88 μM) and the lowest tryptophan value (1.5 μM) of this cohort. The biochemical niacin status of these patients was assessed by the niacin number (Fig. 2D). The average niacin number for the control group was 172.5 ± 9.3 (mean ± SE, n = 24, range: 132–327), and this was not significantly different from the CCS group (158.1 ± 7.1, n = 36, 92–235, $p = 0.284$), or the CWCS group (177.2 ± 10.2, n = 32, 98.9–423.3, $p = 0.546$) (Fig. 2D). In considering the nutrient status of a population, it is usually more important to determine the proportion of a population that falls below a functional cut-off. For niacin number this value is considered to be 130, based on the following four observations: (i) Healthy persons enrolled in a controlled study and eating an unrestricted diet have niacin numbers greater than 130 (range: 132–211) (15); (ii) All the controls in our study also have niacin numbers >130 (range: 132–327); (iii) In a metabolic study, when healthy volunteers were put on a sub-optimal diet of niacin for 3 wks, their average niacin number was 62 (15, 16); and finally (iv) The only pellagrin in our study had a niacin number of 115. Thus, all healthy, niacin-replete persons in controlled studies have niacin numbers above 130, and all known niacin-deficient persons have niacin numbers of less than 130.

Using a niacin number of 130 as a cut-off value, 10 out of 36 CCS patients (28%) were biochemically niacin deficient, while 4 out of 32 CWCS and 0 out of 24 control patients fell below this cut-off. The incidence of niacin deficiency (niacin number below 130) in the CCS population was significantly elevated relative to the control group ($p = 0.004^*$, Fisher's exact test), while the number of patients with niacin deficiency in the CWCS group was not significant ($p = 0.13$).

Interrelationship Between Serotonin, Tryptophan, and Niacin Levels in CCS Patients

To test our hypothesis that increased serotonin production leads to niacin deficiency, we examined whether increase in serotonin values were correlated with decrease in tryptophan and niacin values (Fig. 3). For the entire CCS group of patients, no such linear correlation was observed between serotonin and niacin (Fig. 3A, left panel) or serotonin and tryptophan values (Fig. 3B, left panel). However, this inverse correlation was more apparent in niacin-deficient CCS patients. Using 130 as cut-off limit for niacin number, we divided the 36 CCS patients as biochemically niacin-deficient (CCS-ND, n = 10) or niacin-replete (CCS-NR, n = 26) patients. Interestingly, for the CCS-ND patients, an increase in serotonin values tended to weakly correlate with a decrease in niacin number ($R^2 = 0.17$) and tryptophan levels ($R^2 = 0.12$) (Fig. 3A and B, middle panels). Although the trend indicates a support for our hypothesis, the low correlation coefficient (R^2) values indicate that other parameters may also influence tryptophan and niacin values in the CCS-ND patients. Conversely, for the CCS-NR patients, there was an inverse trend with poor correlation, *i.e.*, as serotonin levels increased, there was an increase in niacin number ($R^2 = 0.03$) as well as tryptophan levels ($R^2 = 0.06$) (Fig. 3A and B, right panels).

DISCUSSION

The niacin status of carcinoid cancer patients has never been systematically evaluated, despite the diagnoses of pellagra and the existence of metabolic conditions that suggest a reduced availability of tryptophan for niacin synthesis. Our study of 68 CCS or CWCS patients shows that sub-clinical niacin deficiency, as defined by a blood niacin number below 130, exists in 28% of CCS patients (10/36), whereas only 1 of these 10 CCS patients was clinically diagnosed with pellagra. Our assessment of 28% of CCS patients suffering from biochemical niacin deficiency at an early stage of the disease is in agreement with a recent report by Bell *et al*. (14), showing that nearly 25% of the patients with advanced malignant carcinoid syndrome develop symptoms of pellagra. Thus, a decrease in niacin number could serve as an early biochemical marker to identify CCS patients who are likely to develop full-blown pellagra at a later stage in the disease.

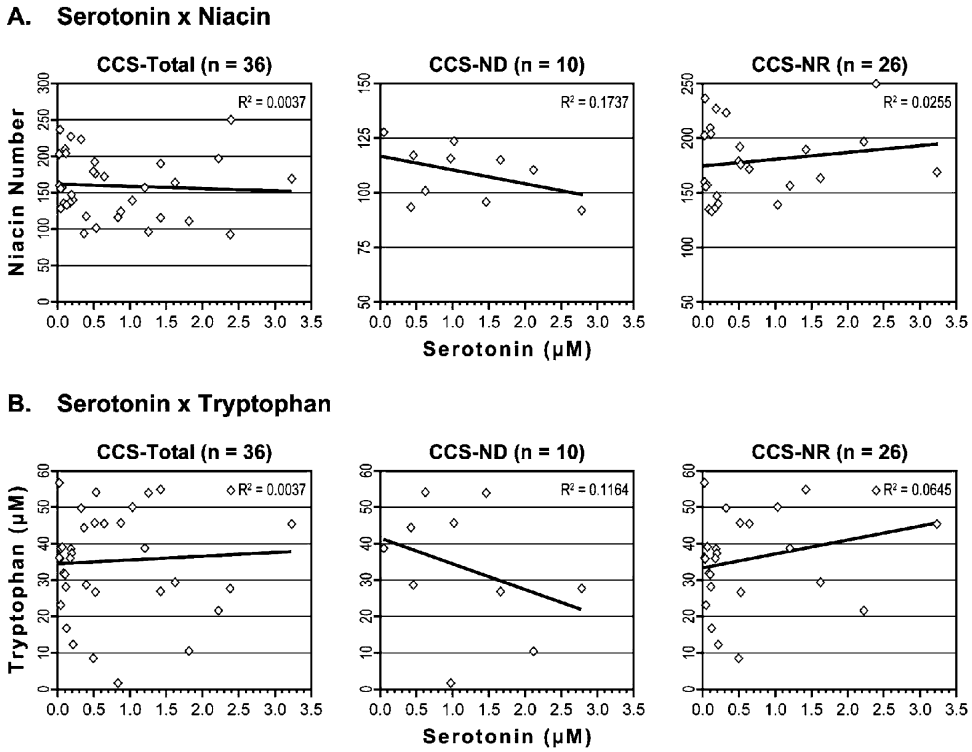

Figure 3. The correlation between serotonin, niacin, and tryptophan levels in CCS patients. All the CCS patients were divided as biochemically niacin-deficient (CCS-ND) or niacin-replete (CCS-NR) patients, based on their niacin number being below or above 130, respectively. In these three groups, *i.e.*, CCS-all (left panels), CCS-ND (middle panels), and CCS-NR (right panels), the correlation between increase in serotonin values and decrease in niacin number (panel A) or tryptophan values (panel B) was examined by linear regression analysis. The trend line is shown with R^2, the regression coefficient.

The question that needs to be addressed is whether detection of biochemical niacin deficiency serves any useful purpose, if the patient is not suffering from clinical symptoms of pellagra. We suggest that it should be done for four possible reasons: (i) Full symptoms of pellagra develop at a very late stage of the carcinoid disease, and it has been shown that 80% of the carcinoid syndrome patients diagnosed with pellagra died soon after this assessment due to advanced stage of the disease (14); (ii) Chances for detection of pellagra are further decreased in carcinoid patients because the full triad of pellagra symptoms develop only in 20% of the noncancerous pellagrins (23) and overlap of symptoms between pellagra and carcinoid syndrome will further decrease the chances for a timely diagnosis of pellagra; (iii) In animal studies, it has been shown that biochemical niacin deficiency increases their susceptibility to nitrosourea-induced leukemia (24–26) and UV-induced skin tumors (27). Thus, a niacin-deficient carcinoid patient may be further susceptible to the adverse impact of DNA damage caused by drugs or radiation used in treatment of the primary carcinoid tumor; and (iv) Finally, sub-clinical niacin deficiency, even without symptoms of pellagra, will still have its biological impact in the cell, just as any deficiency of a vital nutrient. Therefore, an active consideration must be given to early detection of niacin deficiency by biochemical methods.

It is pertinent to note that our study focused on patients who were not taking any vitamin or nutritional supplements at the time of the study. However, it is difficult to completely exclude such nutritional supplements, and various foods are, by law, fortified with niacin. This suggests that our study may have underestimated the true extent of the niacin deficiency problem in carcinoid patients, especially when this disease occurs in areas with lower dietary niacin levels. There is clearly a high variability in the niacin status of carcinoid patients, and this is expected, given that the disease does not directly impact on the utilization of preformed niacin in the diet. Persons with marginal niacin intake from a poor quality diet have a greater dependence on tryptophan conversion and it is these individuals who will be at risk for niacin deficiency when they contract carcinoid-type cancers. Once in the process of the disease, it is known that cancer leads to a high incidence of nutrient deficiencies, including niacin (28), due to changes in food intake and the stresses of disease and treatment on digestion.

In our study, we deliberately excluded patients who were on somatostatin analogs, such as octreotide, in order not to confound the results. However, examination of 5 CCS patients who were on octreotide drug revealed that plasma serotonin levels were decreased to 0.11 ± 0.06 (mean $\pm$ SE) and their niacin number was increased significantly to 180.4 ± 6.3

(n = 5, range: 157–217). It is difficult to generalize based on a small sample size, but it appears that suppression of serotonin levels by octreotide treatment may result in amelioration of the niacin status. More controlled studies of CCS patients before and after the start of octreotide treatment will be required to confirm the effect of octreotide treatment on niacin levels.

It has been shown that giving niacin supplementation to carcinoid patients not only resolves several common symptoms of carcinoid and pellagra, such as skin lesions and diarrhea/steatorrhea, but also generally improves the health of the carcinoid patients (10, 12, 29). Therefore, our results warrant that niacin status should be determined for all carcinoid patients, so that active niacin replacement could be provided to biochemically niacin-deficient patients. In areas of the world where preformed niacin is not added to the food supply and screening of niacin status is not possible, all carcinoid patients should be supplemented with niacin as a preventative therapy.

ACKNOWLEDGMENTS

We are thankful to Dr. R. Giguère (University of Sherbrooke) for analyses of serotonin and tryptophan and Dr. A. Belkacem (Laval University, Quebec) for his help with statistical analyses. H.V. was supported by a summer training scholarship from Canadian Institute of Health Research and Laval University. G.M.S. is a recipient of the FRSQ Chercheur Boursier senior scientist award.

This work was supported by a research operating grant from the Cancer Research Society Inc. of Canada and initially through a start-up research grant from the Carcinoid Cancer Foundation of New York. This work was also supported by an equipment grant from the Natural Sciences and Engineering Research Council of Canada (#252512-02) and the Carcinoid Cancer Foundation of New York.

Reprint requests and correspondence: Girish M. Shah, Ph.D., Laboratory for Skin Cancer Research, CHUL Research Center (CHUQ), 2705, Laurier Boulevard, Room S-16, Sainte-Foy, Quebec, Canada.

Received February 7, 2005; accepted June 13, 2005.

REFERENCES

1. Jensen RT, Norton JA. Carcinoid tumors and the carcinoid syndrome. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and practice of oncology, 5th Ed., Vol. 2. Philadelphia: Lippincott-Raven, 1997:1704–23.
2. Barakat MT, Meeran K, Bloom SR. Neuroendocrine tumours. Endocr Relat Cancer 2004;11:1–18.
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–59.
4. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999;340:858–68.
5. Pasieka JL, McKinnon JG, Kinnear S, et al. Carcinoid syndrome symposium on treatment modalities for gastrointestinal carcinoid tumours: Symposium summary. Can J Surg 2001;44:25–32.
6. Warner RRP. Carcinoid Tumor. In: Berk JE (ed.), Bachus, gastroenterology, 4th Ed., Vol. 3. Philadelphia: W.B. Saunders Company, 1985:1874–86.
7. Ganim RB, Norton JA. Recent advances in carcinoid pathogenesis, diagnosis and management. Surg Oncol 2000;9:173–9.
8. Kirkland JB, Rawling JM. Niacin. In: Rucker RB, Suttie JW, McCormick DB, Machlin LJ (eds.), Handbook of vitamins, 3rd Ed. New York: Marcel Dekker Inc., 2001:213–54.
9. Ikeda M, Tsuji H, Nakamura S, et al. Studies on the biosynthesis of nicotinamide adenine dinucleotide. II. A role of picolinic carboxylase in the biosynthesis of nicotinamide adenine dinucleotide fom tryptophan in mammals. J Biol Chem 1965;240:1395–401.
10. Fleischmajer R, Hyman AB. Clinical significance of derangements of tryptophan metabolism: A review of pellagra, carcinoid and H disease. Arch Dermatol 1961;84:563–73.
11. Thorson A, Biorck G, Bjorkman G, et al. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis; a clinical and pathologic syndrome. Am Heart J 1954;47:795–817.
12. Swain CP, Tavill AS, Neale G. Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra, and hypoproteinemia. Gastroenterology 1976;71:484–9.
13. Castiello RJ, Lynch PJ. Pellagra and the carcinoid syndrome. Arch Dermatol 1972;105:574–7.
14. Bell HK, Poston GJ, Vora J, et al. Cutaneous manifestations of the malignant carcinoid syndrome. Br J Dermatol 2005;152:71–5.
15. Jacobson EL, Jacobson MK. Tissue NAD as a biochemical measure of niacin status in humans. Methods Enzymol 1997;280:221–30.
16. Fu CS, Swendseid ME, Jacob RA, et al. Biochemical markers for assessment of niacin status in young men: Levels of erythrocyte niacin coenzymes and plasma tryptophan. J Nutr 1989;119:1949–55.
17. Benyon S, ed. Nutrition. London: Mosby, 1998:125–46.
18. Shah GM, Poirier D, Duchaine C, et al. Methods for biochemical study of poly(ADP-ribose) metabolism in vitro and in vivo. Anal Biochem 1995;227:1–13.
19. Markey SP, Boni RL, Yergey JA, et al. Mass spectrometric determinations of tryptophan and its metabolites. Adv Exp Med Biol 1991;294:41–50.
20. Davidson DF. Simultaneous assay for urinary 4-hydroxy-3-methoxy-mandelic acid, 5-hydroxyindoleacetic acid and homovanillic acid by isocratic HPLC with electrochemical detection. Ann Clin Biochem 1989;26(Pt 2):137–43.
21. Agresti A, (ed.) Categorical data analyses. New York: Wiley, 1990.
22. Lentner C. Blood-nitrogenous substances. In: Lentner C, Lentner C, Wink A (eds.), Geigy scientific tables: Physical chemistry: Composition of blood, hematology, somatometric data, 8th Ed., Vol. 3. Basle: CIBA-GEIGY Limited, 1984:89–106.
23. Spivak JL, Jackson DL. Pellagra: An analysis of 18 patients and a review of the literature. Johns Hopkins Med J 1977;140:295–309.
24. Boyonoski AC, Gallacher LM, ApSimon MM, et al. Niacin deficiency in rats increases the severity of

ethylnitrosourea-induced anemia and leukopenia. J Nutr 2000;130:1102–7.
25. Boyonoski AC, Spronck JC, Gallacher LM, et al. Niacin deficiency decreases bone marrow poly(ADP-ribose) and the latency of ethylnitrosourea-induced carcinogenesis in rats. J Nutr 2002;132:108–14.
26. Spronck JC, Kirkland JB. Niacin deficiency increases spontaneous and etoposide-induced chromosomal instability in rat bone marrow cells in vivo. Mutat Res 2002;508:83–97.
27. Shah GM, Le Rhun Y, Sutarjono I, et al. Niacin deficient SKH-1 mice are more susceptible to ultraviolet B radiation-induced skin carcinogenesis. J Nutr 2001;131:3150S.
28. Inculet RI, Norton JA, Nichoalds GE, et al. Water-soluble vitamins in cancer patients on parenteral nutrition: A prospective study. JPEN J Parenter Enteral Nutr 1987;11:243–9.
29. Warner RR. Carcinoid case presentation and discussion: The American perspective. Endocr Relat Cancer 2003;10:489–96.