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Liver and Kidney Biochemical Profile of Typhoid Fever Patients at the Dschang District Hospital, West Cameroon: A Cross-Sectional Study

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Abstract

Background: Typhoid fever remains prevalent in developing countries and most often affects liver and kidney. This study aimed to assess biochemical disturbances of the liver and kidney in patients with typhoid fever at the Dschang District Hospital, appreciate the implication of the disease duration as well as the type and the duration of treatment.

Methods and materials: This cross-sectional study was conducted at the Dschang District Hospital, Cameroon. A total of 263 participants and a structure questionnaire was used to collect sociodemographic data. Stool culture was used for the diagnosis of typhoid fever. Liver and kidney biomarkers were access using spectrophotometric technic.

Results: By these technics, 112 healthy individuals (Control Group, CG), and 151 patients diagnosed with typhoid fever (Study Group, SG) were obtained. A significant lower level of albumin ($p<0.05$) was noted in SG compare to CG while other biochemical parameters of the liver and kidney function (ALT, AST, T-BILI, C-BILI, ALP, γ-GT, urea and creatinine) presented a significant higher levels at varying degrees, especially for ALT ($p <0.001$), AST, ALP, urea and creatinine ($p <0.01$), T-BILI, C-BILI and γ-GT ($p <0.05$).

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Relatively to the variation of biochemical parameters with respect to the duration of illness in the patients before their arrival to the hospital, except albumin which had a significant ($p<0.05$) decreased level from the first to the third week of the disease, ALT and AST had a significant ($p<0.05$) increased level from the first to the third week of the disease and, T-BILI, C-BILI, UC-BILI, ALP and γ-GT from the second to the third week of the disease. Relatively to the type of drug intake, the serum level of ALT, **γ**-GT, albumin and creatinine were significantly increased ($p<0.05$) with fluoroquinolones and indigenous (medicinal plants) intake while the serum level of AST, T-BILI, C-BILI, UC-BILI, ALP, urea and creatinine clearance were significantly ($p<0.05$) increased only with indigenous intake. Relatively to the duration of treatment, except creatinine clearance that significantly ($p<0.05$) decreased at the third week of treatment, the serum level of ALAT, ASAT, C-BILLI, ALP, γ-GT and albumin were significantly ($p<0.05$) increased from the first to the third week of the treatment, the serum level of T-BILI, UC-BILI and urea from the second to the third week of the treatment, and the serum level of creatinine at the third week of the treatment. There was a significant correlation between disease duration, drug intake duration and the serum level of ALT, AST, total bilirubin, conjugated bilirubin, unconjugated bilirubin, ALP, γ-GT, urea, creatinine, albumin and creatinine clearance.

Conclusion: The results of this study suggest that typhoid fever negatively affects the proper functioning of the liver and kidneys, which varies depending on the duration of the illness, self-medication with conventional drugs such as fluoroquinolones and medicinal plants, and the duration of treatment.

Keywords: Typhoid fever; Biomarkers; Hepatotoxicity; Nephrotoxicity.

1. Introduction

Typhoid fever is an enteric disease caused by the ingestion of water or food contaminated with *salmonella enterica* serotype Typhi. It remains an important public health problem in the world especially in the impoverished population from developing countries, because this substantial proportion of the population does not have access to improved drinking water, sanitation and to wholesome food [1]. Typhoid fever affects one or more major organs of the body resulting from a broad spectrum of infections such as hepatitis, gastroenteritis, myocarditis, glomerulonephritis associated or not with acute renal failure or tubular necrosis [2]. The liver or the kidney of patients suffering from typhoid fever is usually affected and the pathogenesis of the involvement of these organs remains uncertain[3]. It could be caused by endotoxin secreted by *Salmonella typhi* during it lysis. This bacteria induce cholestasis that may result from the invasion of the livercausing the damage of the hepatobiliary system. Moreover, hepatic cells (mainly Küpffer cells) are targets of endotoxin and will secrete cytokines such as TNF-α, a marker of its necrosis [4]. In patients with typhoid fever, a diffuse proliferative glomerulonephritis has been defined on light microscopic examination of renal biopsy materials and immunoglobulin, C3 complement and *Salmonella Typhi* Vi antigens have been detected on immunoflourescent examination [5], indicating that renal damage is either immunological or directly caused by *Salmonella typhi*. There is an increased risk of developing these organic lesions with a prolonged typhoid fever duration before hospitalization [6]. These organic lesions are evidenced by the variation of the serum level of biochemical markers of hepatotoxicity (transaminases, bilirubin, alkaline phosphatase, gamma glutamyl transferase and albumin) and nephrotoxicity (creatinine, urea) [7,8]. During the treatment of typhoid fever, antibiotics such as

fluoroquinolones (ciprofloxacin, ofloxacin) are often used [9]. However, in the long-term use of these drugs or at higher doses, the quantity in the body is important and can cause toxic effects in several organs, including the liver (hepatotoxicity) and kidneys (nephrotoxicity) [10]. Thus, in the liver, the metabolism of fluoroquinolones would generate oxidative radicals, which could induce DNA damage or mitochondrial damage leading to hepatocellular damage manifested as hepatitis, jaundice, liver injury and hepatic failure. Fluoroquinolones induced hepatotoxicity were marked by elevated levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, direct bilirubin, total bilirubin and gamma glutamyl transferase [11]. Fluoroquinolones also have the ability to inhibit, in a competitive manner, the transport of creatinine by human organic cation transporter 2 (hOCT2) which is the most abundant organic cation transporter so far reported in the human kidney [12]. Long-term use of fluoroquinolones or at higher doses lead to a significant inhibition of tubular secretion of creatinine and consequently elevating serum creatinine level with no or apparent change of urea serum level [13]. Knowing that in our locality, prolonged typhoid fever duration are frequent and self-medication by conventional drugs or medicinal plants is a common practice, patients would be potentially exposed to liver and kidney damage. Thus, this study had as objective to assess biochemical disturbances of the liver and kidney in patients with typhoid fever at the Dschang District Hospital, appreciate the implication of the disease duration as well as the type and the duration of treatment.

2. Materials and methods

2.1. Study design and population

This study was a cross-sectional study conducted at the Dschang District Hospital in Cameroon. The questionnaires were distributed to all patient suspected of having typhoid fever by the doctor following clinical diagnosis (fever, headache, diarrhea, constipation, vomiting, abdominal pain, lack of appetite and nocturnal insomnia) and healthy individuals (control group). Inclusion criteria used for the control group (CG) was persons confirmed by stool examination that had never suffered from typhoid fever while patients included in the study group (SG) were patients diagnosed with typhoid fever by stool culture. Exclusion criteria for both groups were positive status for viral hepatitis (A, B or C), active alcohol consumption, and malaria, history on liver or kidney diseases, obesity, diabetes and hypertension. After that, two hundred and sixty three (263) participants were considered in the study. CG consisted of 112 healthy individuals, while 151 were taken as SG.

2.2. Stool and blood sampling

Twenty to 30 g of stool were collected in wide-mouthed plastic container from each participant included in the study for stool culture. 5 ml of venous blood were collected in the dry tubes from participants, allowed to rest for 30 minutes and centrifuged at 5000 rpm for 10 minutes to obtain sera that were used for liver and kidney functions tests as investigation tests.

2.3. Stool culture

Three to 5 g of stool collected from each participant were diluted in 5 ml of NaCl sterile solution (0.9%) to obtain the inoculum. A portion of each inoculum was used for microscopic examination (gram staining) to

evaluate the percentage of Gram positive and Gram-negative bacteria. Another part was seeded on Salmonella-Shigella (SS) agar and 1 ml was introduced into 9 ml of selenite broth for an enrichment culture. Both preparations were incubated aerobically at 37°C for 24 hours after which the incubated SS plate was observed. In case of bacterial growth (presence of colonies), subculture of the previously enriched selenite and stool mixture was made on a new SS medium and re-incubated at 37°C for 24 hours. After observation, colonies suspected to be salmonella (black center colonies) were biochemically characterized using the Api 20E gallery to identify the salmonella type.

2.4. Biochemical analyses

From sera collected, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T-BILI), conjugated bilirubin (C-BILI), unconjugated bilirubin (UC-BILI), alkaline phosphatase (ALP), gamma-glutamyltransferase (γ-GT) and albumin levels were measured to assess liver function while urea and creatinine were quantified to evaluate renal function. The measurements were performed on DÎALAB DTN-405 Chemistry Analyzer (*DÎALAB Produktion und Vertrieb von chemisch-technischen Produkten und Laborinstrumenten, Austria*) using standard DÎALAB® commercial kits.

2.5. Ethical approval

The National Committee of Ethical Research in Human Health (NCERH) of Cameroon approved our study under reference ethical number 2019/03/07/CE/CNERSH/SP of 14 March 2019, and informed consent was obtained from each participant. The data regarding age, sex, duration of illness, type and duration of medication were obtained from each participant before sample collection.

2.6. Statistical analyses

Data collected was analyzed using the software IBM SPSS version 22. Results were expressed as mean ± standard deviation. Student conformity test were used to compare variables' means in CG to reference values. Independent sample t-tests were used for comparisons of variables between typhoid fever and healthy individuals. Two-way ANOVA and Student-Newman-Keuls Post-hoc test, were applied to determine the difference between groups. Sex was taken as covariate because it was a confounding factor in the variation of liver and kidney biochemical parameters studied. Pearson's correlation analysis for the required biochemical parameters was performed to determine associations between these parameters and some factors. The alpha significance level was 5%.

3. Results

The mean age of participant in the study group (SG) was 26.56 ± 10.37 years and 25.76 ± 9.87 years in the control group (CG). Males were more frequent in CG (38.41% or 58/151) than in the SG (23.18% or 35/151). In contrast, females were more frequent in SG (76.82% or 116/151) than in CG (61.59% or 93/151). The minimum duration of illness before patients came to the hospital was 2 days while the maximum duration was 38 days. Concerning the duration of drug intake, it was 2 days for the minimum duration and 21 days for the maximum

duration.

Table 1 shows the comparison of biochemical parameters of liver and kidney functions tests between the SG and the CG. From the analysis of these data, the mean values of ALT, AST, T-BILI, C-BILI, UC-BILI, ALP, γ-GT, albumin, urea, creatinine and creatinine clearance in the CG were within range of the reference values. All of these values except albumin and creatinine clearance were significantly ($p<0.05$) higher in the SG as compared to the CG.

Table 1: Comparison of biochemical parameters of liver and kidney functions tests between study group and control group

Parameters	**CG (n=112)**	**SG (n= 151)**	**Reference value**	***P-value***
Liver				
ALT	15.62 ± 4.28*	49.21 ± 22.43	< 34 g/dl	**0.00**
AST	22.04 ± 6.72*	39.92 ± 15.44	< 31 g/dl	**0.00**
T-BILI	0.56 ± 0.21*	1.38 ± 1.38	0.2-1.0 mg/dl	**0.01**
C-BILI	0.11 ± 0.08*	0.29 ± 0.53	0.0-0.2 mg/dl	**0.04**
UC-BILI	0.45 ± 0.19*	1.09 ± 1.31	0.2-0.8 mg/dl	**0.07**
ALP	121.17 ± 45.71*	277.51 ± 110.00	< 258 UI/l	**0.00**
γ-GT	15.05 ± 4.94	54.33 ± 34.51	Women : < 32 UI/l, Men :<49 UI/l	**0.03**
Albumin	4.00 ± 0.38*	3.47 ± 1.93	3.5 à 5.2 g/dl	**0.03**
Kidney				
Urea	23.77 ± 7.88*	46.68 ± 32.25	Women: [15-40 mg/dl], Men:[19-44 mg/dl]	**0.00**
Creatinine	64.17 ± 10.82*	144.56 ± 125.52	Women: [53-97 µmol/l], Men :[62-115 µmol/l]	**0.00**
Creatinine Clearance	128.31 ± 41.45*	83.70 ± 41.93	>90 ml/min	**0.00**

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T BILI = Total bilirubin, C BILI = Conjugated bilirubin, UC BILI = Unconjugated bilirubin, ALP = Alkaline phosphatase, γ-GT = Gamma Glutamyl Transferase.SG = Study Group, CG = Control Group; n = number of participants per group. p = probability. Stars indicates means in CG that are significantly different from reference values. Sex is taken as covariate in the 2-way ANOVA model. Stratified means are not presented.*

Table 2 presents the influence of typhoid fever duration on the biochemical parameters of liver and kidney functions on patients without medication. Except albumin and creatinine clearance that have a significant ($p<0.05$) decreased depending on the duration of the disease, all the other biochemical parameters significantly

($p<0.05$) increased at varying degrees. Thus, some biochemical parameters increased from the first to the third week of the disease (ALAT and ASAT). Others biochemical parameters increased from the second to the third week of the disease (T-BILI, C-BILI, UC-BILI, ALP and γ-GT). The increased in urea and creatinine became significant ($p<0.05$) from the third week of the disease.

Table 2: Variation of biochemical parameters of liver and kidney functions with respect to the disease duration

Parameters	**CG (n=112)**	**≤ 1week (n = 57)**	**]1 to 2 weeks] (n = 49)**	**≥ 3 weeks (n =21)**	**Reference value**	***P-value***
	Liver					
ALT	15.62±4.28^{a}	40.28 ± 18.06^{b}	45.01 ± 20.99^{b}	58.02 ± 16.66^{c}	< 34 g/dl	**0.02**
AST	22.04±6.72^{a}	34.29 ± 12.77^{b}	38.02 ± 13.61^{b}	43.51 ± 12.92^{c}	< 31 g/dl	**0.01**
T-BILI	0.56±0.21^{a}	0.97 ± 0.67^{b}	1.12 ± 0.71^{b}	1.47 ± 0.80^{c}	0.2-1.0 mg/dl	**0.00**
C-BILI	0.11±0.08^{a}	0.22 ± 0.33^{b}	0.15 ± 0.15^{ab}	0.38 ± 0.35^{c}	0.0-0.2 mg/dl	**0.00**
UC-BILI	0.45±0.19^{a}	0.74 ± 0.56^{b}	0.96 ± 0.70^{c}	1.08 ± 0.92^{c}	0.2-0.8 mg/dl	**0.03**
ALP	121.17±45.71^{a}	227.67 ± 76.63^{b}	273.72 ± 73.77^{c}	291.69 ± 70.09^{c}	< 258 UI/l	**0.00**
γ-GT	15.05±4.91^{a}	40.41 ± 22.84^{b}	52.13 ± 28.23^{c}	60.05 ± 26.12^{d}	Women : < 32 UI/l, Men :<49 UI/l	**0.00**
Albumin	4.00±0.38^{a}	3.12 ± 1.11^{b}	2.82 ± 1.17^{b}	2.17 ± 1.26^{c}	3.5 à 5.2 g/dl	**0.00**
	Kidney					
Urea	23.77±7.88^{a}	35.48 ± 19.48^{b}	38.52 ± 23.23^{b}	61.96 ± 27.83^{c}	Women: [15-40 mg/dl], Men:[19-44 mg/dl]	**0.01**
Creatinine	64.17±10.82^{a}	99.16 ± 60.73^{b}	106.53 ± 65.76^{b}	206,44 ± 136,13^{c}	Women: [53-97 µmol/l], Men :[62-115 µmol/l]	**0.00**
Creatinine Clearance	128.31±41.45^{a}	95.19 ± 32.55^{b}	91.10 ± 38.68^{b}	69.19 ± 38.84^{c}	>90 ml/min	**0.01**

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T-BILI = Total bilirubin, C-BILI = Conjugated bilirubin, UC-BILI = Unconjugated bilirubin, ALP = Alkaline phosphatase, γ-GT = Gamma Glutamyl Transferase. ^{a,b,c,d} *= Assigned values with different letters are significantly different by comparing the values of different groups at a reference probability level of 5% in the 2-way ANOVA model. Sex is taken as covariate. Stratified means are not presented. n = number of participants per group. p = probability* Relatively to the questionnaires submitted to the participants upon their arrival at the hospital, some of them were under self-medication based either on pharmaceutical molecules (fluoroquinolones) or on medicinal plants (decoctions of *Curcuma longa*; *Mangifera indica*; *Cola acuminata*). **Table 3** presents the profile of biochemical parameters of liver and kidney functions with respect to the types of drugs intake by the patients before their arrival in the hospital. Compared to the patients without medication, all the biochemical parameters were significantly increased with indigenous intake, except creatinine clearance, that significantly ($p<0.05$) decreased with indigenous intake. However, some biochemical parameters significantly increased ($p<0.05$) with

fluoroquinolones and indigenous intake (ALT, γ-GT, albumin and creatinine) while other significantly ($p<0.05$) increased only with indigenous (AST, T-BILI, C-BILI, UC-BILI, ALP, urea and creatinine clearance).

Table 3: Profile of biochemical parameters of liver and kidney functions with respect to type of drug consumed

Parameters	Patients without medication (n=127)	Fluoroquinolones (n=13)	Indigenous* (n=11)	Reference value	*P-value*
	Liver				
ALT	45.04±19.88[a]	62.65 ± 15.32[b]	81.45 ± 26.24[c]	< 34 g/dl	**0.01**
AST	37.25±13.43[a]	44.37 ± 8.80[a]	65.38 ± 19.52[b]	< 31 g/dl	**0.00**
T-BILI	1.11±0.72[a]	1.68 ± 1.75[a]	4.17 ± 2.97[b]	0.2-1.0 mg/dl	**0.00**
C-BILI	0.22±0.29[a]	0.54 ± 0.93[ab]	0.76 ± 1.32[b]	0.0-0.2 mg/dl	**0.04**
UC-BILI	0.88 ± 0.69[a]	1.14 ± 1.65[a]	3.41 ± 3.14[b]	0.2-0.8 mg/dl	**0.00**
ALP	256.02 ± 78.49[a]	302.65 ± 159.90[a]	495.84 ± 118.65[b]	< 258 UI/l	**0.04**
γ-GT	48.18 ± 26.47[a]	69.55 ± 54.62[b]	107.30 ± 39.92[c]	Women : < 32 UI/l, Men :<49 UI/l	**0.00**
Albumin	2.84 ± 1.20[a]	5.78 ± 1.69[b]	7.93 ± 0.91[c]	3.5 à 5.2 g/dl	**0.00**
	Kidney				
Urea	41.03 ± 24.21[a]	57.98 ± 43.90[a]	98.55 ± 43.90[b]	Women: [15-40 mg/dl], Men:[19-44 mg/dl]	**0.02**
Creatinine	119.74 ± 87.98[a]	199.00 ± 173.99[b]	366.79 ± 191.00[c]	Women: [53-97 µmol/l], Men :[62-115 µmol/l]	**0.00**
Creatinine Clearance	88.76 ± 37.51[a]	77.54 ± 60.32[a]	32.55 ± 32.09[b]	>90 ml/min	**0.00**

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T-BILI = Total bilirubin, C-BILI = Conjugated bilirubin, UC-BILI = Unconjugated bilirubin, ALP = Alkaline phosphatase, γ-GT = Gamma Glutamyl Transferase. [a,b,c] *= Assigned values with different letters are significantly different by comparing the values of different groups at a reference probability level of 5% in the 2-way ANOVA model. Sex is taken as covariate. Stratified means are not presented. n = number of participants per group. p = probability. *Decoction of Curcuma longa*; *Mangifera indica*; *Cola acuminata*

Table 4 summarizes the influence of treatment duration on the biochemical parameters of the liver and kidney

functions. It appears that, compared to the patients without medication, except creatinine clearance that significantly (*p<0.05*) decreased at the third week of treatment, all the other biochemical parameters significantly (*p<0.05*) increased at varying degrees. Thus, some biochemical parameters significantly (*p<0.05*) increased from the first to the third week of the treatment (ALAT, ASAT, C-BILLI, ALP, γ-GT, albumin). T-BILI, UC-BILI and urea significantly (*p<0.05*) increased from the second to the third week of treatment, while creatinine significantly (*p<0.05*) increased at the third week of the treatment.

Table 4: Variation of biochemical parameters of liver and kidney functions with respect to drug intake duration

Parameters	**Patients without medication (n=127)**	**≤ 1week (n= 8)**	**]1 to 2 weeks] (n= 7)**	**]2 to 3 weeks] (n=9)**	**Reference value**	***P-value***
	Liver					
ALT	45.04±19.88[a]	55.38 ± 5.53[ab]	71.49 ± 4.21[b]	85.22 ± 31.06[b]	< 34 g/dl	**0.03**
AST	37.25±13.43[a]	43.09 ± 7.71[ab]	51.25 ± 7.77[b]	65.83 ± 23.26[c]	< 31 g/dl	**0.00**
T-BILI	1.11±0.72[a]	1.24 ± 1.26[a]	2.15 ± 2.20[b]	4.76 ± 2.85[c]	0.2-1.0 mg/dl	**0.00**
C-BILI	0.22±0.29[a]	0.85 ± 1.11[b]	0.62 ± 1.26[ab]	0.48 ± 1.09[ab]	0.0-0.2 mg/dl	**0.00**
UC-BILI	0.88 ± 0.69[a]	0.39 ± 0.23[a]	1.53 ± 1.99[b]	4.27 ± 2.97[c]	0.2-0.8 mg/dl	**0.03**
ALP	256.02 ± 78.49[a]	334.90 ± 169.06[b]	381.09 ± 221.17[ab]	449.10 ± 122.57[c]	< 258 UI/l	**0.00**
γ-GT	48.18 ± 26.47[a]	79.90 ± 51.75[b]	83.46 ±57.35[b]	95.67 ± 50.72[b]	Women : < 32 UI/l, Men :<49 UI/l	**0.00**
Albumin	2.84 ± 1.20[a]	6.00 ± 1.53[b]	6.78 ± 1.89[ab]	7.35 ± 1.72[c]	3.5 à 5.2 g/dl	**0.03**
	Kidney					
Urea	41.03 ± 24.21[a]	49.69 ± 30.38[a]	82.92 ± 70.43[b]	95.54 ± 37.25[b]	Women: [15-40 mg/dl], Men:[19-44 mg/dl]	**0.01**
Creatinine	119.74 ± 87.98[a]	166.05 ± 122.93[a]	204.83 ± 173.76[a]	428.83 ± 182.53[b]	Women: [53-97 µmol/l], Men :[62-115 µmol/l]	**0.01**
Creatinine Clearance	88.76 ± 37.51[a]	79.25 ± 58.03[a]	67.00 ± 53.88[a]	29.22± 40.98[b]	>90 ml/min	**0.01**

ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, T-BILI = Total bilirubin, C-BILI = Conjugated bilirubin, UC-BILI = Unconjugated bilirubin, ALP = Alkaline phosphatase, γ-GT = Gamma Glutamyl Transferase. [a,b,c,d] *= Assigned values with different letters are significantly different by comparing the values of different groups at a reference probability level of 5% in the 2-way ANOVA model. Sex is taken as covariate. Stratified means are not presented. n = number of participants per group. p = probability*.

Table 5 shows the different correlation coefficients of hepatotoxicity and nephrotoxicity parameters with some factors (duration of illness and the duration of medication). The levels of ALT, AST, T-BILI, C-BILI, UC-BILI, ALP, γ-GT, albumin, urea and creatinine were positively and significantly correlated with the duration of illness and with the duration of medication while creatinine clearance was negatively and significantly correlated with those factors. For each biochemical parameters studied, the correlation coefficient was higher in relation with the duration of medication than the duration of illness.

Table 5: Correlation (r-value) of biochemical parameters of hepatic and renal function with respect to the durations of illness and medication

Parameters	Duration of illness	Duration of medication
Liver		
ALT	0.345**	0.490**
AST	0.285**	0.486**
T-BILI	0.332**	0.623**
C-BILI	0.214**	0.211**
UC-BILI	0.264**	0.573**
ALP	0.403**	0.523**
γ-GT	0.335**	0.417**
Albumin	0.015**	0.680**
Kidney		
Urea	0.490**	0.486**
Creatinine	0.596**	0.588**
Creatinine Clearance	-0.419**	-0.352**

** = correlation is significant at the 0.05 level (p<0.05); ** = correlation is significant at the 0.01 level (p<0.01).*

4. Discussion

Typhoid fever remains prevalent in developing countries due to the poor socio-economic and hygienic conditions of the population. This disease most often affects liver and/or kidney [3]. The present study aimed at evaluating biochemical disturbances of the liver and kidney in patients with typhoid fever at the Dschang District Hospital, appreciate the implication of the disease duration as well as the type and the duration of treatment. Globally, except albumin and creatinine clearance, all of the biochemical parameters studied increased in patients than in controls. The severity of these observed trends increases with the duration of the disease. In Nigeria, Ozougwu and his colleagues [14] obtained the same results for the change in renal biochemical parameters with a significant increase of serum urea and creatinine level. In India, Srikanth and Kumar [15] conducted a similar study and obtained the same results with a significant increase of ALT, AST, direct/total bilirubin and ALP concentrations and a significant decrease of albumin. In Iraq, Shawki and Jameel [16] achieved similar results with a significant increase of ALT, AST, ALP, total bilirubin and blood urea. Thus, these studies confirm that typhoid fever negatively affect liver and kidney functions. The mean level of ALT and AST were higher in the SG than the CG. But, the mean level of ALT was higher than that of AST in the SG. Indeed, ALT is found in high concentrations in hepatocytes and at very low concentrations in other tissues, AST is present in many other tissues than the liver particularly the muscles (cardiac, skeletal and smooth muscles),

kidney and brain. Thus, the increased level of ALT than AST observed in the SG characterizes liver damage and confirms that ALT is a more specific marker of liver injury than ASAT [17]. . The high serum level of ALAT and AST obtained in our study could be due to hepatocyte necrosis, which is characterized by the destruction of hepatocytes by reactive oxygen species (ROS) initially intended for the destruction of *Salmonella typhi* in the liver [18,19]. Indeed, during the evolution of typhoid fever, *Salmonella typhi* leaves the intestinal lumen by infecting lymphoid tissues via the lymphatic circulation to end up in the macrophages of the liver (Küpffer cells) where it multiplies there and spreads into the body through the bloodstream to colonize the kidney [4,19]. The lysis of a part of *Salmonella typhi* in the lymph nodes releases the endotoxin (very toxic lipopolysaccharides) which is carried by the blood to the liver. In the liver, Küpffer cells are activated by these lipopolysaccharides and secrete cytokines (TNF-α, IL-1, IL-6) which induce the production of ROS that destroy Salmonella typhi by necroptosis (programmed necrosis), would also destroy the hepatocytes [18]. Given that the number of apoptotic hepatocytes would be proportional to the dose of endotoxin secreted by *Salmonella typhi* during it lysis [20], the increase in serum biochemical parameters of the liver would be explained by the increase in the dose of endotoxin during the increase of the duration of disease. The liver damage that we founded via the increased level of ALT than that of AST was further confirmed by the total bilirubin, ALP, γ-GT and albumin levels. The significant increased in total bilirubin and conjugated bilirubin serum level in the SG than the CG indicated the disturbance of the liver secretion function (hepatocellular dysfunction) in typhoid fever patients. This would be less due to hemolysis but more to canalicular occlusion by the swollen hepatocytes. This may be followed by focal hepatocellular necrosis which can promote rupture of bile canaliculi leading to direct reflux of bile into the hepatic sinusoids, hence the increase in conjugated bilirubin [21]. High values of ALP and transaminases observed in the SG indicated the involvement of hepatobiliary system which may be secondary to an endotoxic effect on the hepatic parenchyma causing edema and biliary stasis. Typically, alkaline phosphatase level in serum increases with obstruction of the bile ducts that can be due to the presence of *Salmonella typhi* [22]. In fact, bile duct obstruction results in increased synthesis of ALP by bile duct epithelial cells and release of ALP into the serum. Alkaline phosphatase may be increased even if only a few small bile ducts are obstructed and serum bilirubin is normal [17,23]. Alkaline phosphatase is not only on the canalicular membrane of the hepatocyte. It is also found in bone, placenta, intestine, and kidney. Thus, to confirm hepatic origin of alkaline phosphatase, the canalicular enzyme γ-GT may be measured. An elevated γ-GT suggests that the alkaline phosphatase elevation is from hepatic origin [23]. The γ-GT level was significant increased in the SG than the CG and then allowing us to confirm that the increased level of alkaline phosphatase was hepatic origin. The increase in activity of enzyme γ-GT would mainly due be to an induction of its expression in the bile ducts and undoubtedly, as for alkaline phosphatases, of its release to the canalicular membrane of the hepatocyte by the detergent action of bile acids indicating cholestasis due to *Salmonella typhi* [24]. Albumin synthesis is predominantly take place in the hepatocytes [25]. Hypoalbuminemia observed could be explained by a decreased synthesis of albumin. In fact, hepatocyte necrosis, which occurs in liver during typhoid fever, releases the contents of hepatocytes, including albumin-synthesizing enzymes, thereby resulting probably to a deficit in albumin synthesis as a result of the liver synthesis function disturbance. Urea and creatinine levels obtained were significantly higher in SG than CG. It is known that urea is a nitrogen-containing compound formed in the liver as end product of protein catabolism, and about 85% of urea is eliminated via the kidneys and the rest is excreted via the gastrointestinal tract [7]. Thus, serum urea is increased in conditions where renal clearance

decreased. But the most commonly used endogenous marker for assessment of glomerular function is creatinine which is the by-product of creatine phosphate in muscle, and it is produced at a constant rate by the body. Generally, creatinine is commonly cleared from the blood entirely by the kidney [7]. The significant increase in the serum level of urea and creatinine indicated impaired kidney function [26]. It was confirmed by the decreased in creatinine clearance, indicating a glomerular dysfunction of kidney. The significant increased in creatinine level and the significant decreased in creatinine clearance observed at the third week of the disease could indicate that kidney is not always involved in typhoid fever but can be regarded as a complication. However, although the pathogenesis of kidney damage due to typhoid fever remains unclear, it could be immunological or directly caused by *Salmonella typhi*. These two theories have been confirmed by kidney biopsy of typhoid fever patients who show diffuse proliferative glomerulonephritis with IgM deposits, C3 complement and Vi antigen in the wall of capillaries of damaged glomeruli [5]. We found that treatment of typhoid fever with medicinal plants (indigenous) caused more hepatotoxicity and nephrotoxicity than treatment with fluoroquinolones. In their study, Gulati and his colleagues [27] have demonstrated that the transformation of drugs in the liver (hepatocyte) generates reactive metabolites that can interact directly with proteins, lipids or nucleic acids to initiate oxidative stress leading to hepatocyte necrosis, independently to the duration of drug intake. The hyperalbuminemia observed from the first to the third week of treatment could be due to liver albumin production for the transport of drugs. It has been demonstrated that, Human serum albumin regulates the transport and availability of numerous chemical compounds and molecules in the blood vascular system such as drugs [28]. Concerning the kidney function, it was affected at the third week of the treatment. In fact, prolonged treatment could affect the functioning of the kidneys due to the accumulation of reactive oxygen species (ROS) in the kidneys that can lead to oxidative stress and lead to necrosis in the kidney tissue, causing renal biochemical changes [29]. Concerning the use of fluoroquinolones in the treatment of typhoid fever, it had been shown that those drugs have the ability to inhibit, in a competitive manner, the transport of creatinine by human organic cation transporter 2 (hOCT2) which is the most abundant organic cation transporter so far reported in the human kidney [12]. Long-term use of fluoroquinolones or at higher doses also lead to a significant inhibition of tubular secretion of creatinine and consequently elevating serum creatinine level with no or apparent change of urea serum level [13], and by this causing a glomerular dysfunction of the kidney. The use of medicinal plants in the treatment of diseases is almost universal and is cheaper than conventional drugs. This treatment method in typhoid fever or others diseases would be effective but requests more caution. Natural plants contain phyto-constituents containing chemical properties similar to those of synthetic antibiotics such as chloramphenicol for the treatment of typhoid fever [30]. Unfortunately, the dosage of these decoctions is not very often precise, and can therefore expose the patient to a long-term overdose with the consequence of the involvement of several organs among which the liver and kidney [31]. The maximum duration of illness (38 days) was almost twice higher than the maximum duration of medication (21 days), and not all patients were on medication. However, the correlation coefficient was very high in relation to the duration of medication than the duration of the disease. This could be explained by an increase in hepatotoxicity or nephrotoxicity due to the combined effect of the endotoxin released during *Salmonella typhi* lysis and the metabolism of drugs consumed. This study provided the first data concerning the liver and kidney biochemical dysfunctions induce by *Salmonella typhi* in Cameroon. The non-measurement of endotoxin or lipopolysaccharide (LPS) level in blood, secreted cytokine (TNF-α, IL-1, IL-6) induce by endotoxin, and reactive oxygen species (ROS) which can lead

to necrosis in the liver or kidney were the main limitations of this study.

5. Conclusion

The aim of this study was to assess biochemical disturbances of the liver and kidney in patients with typhoid fever at the Dschang District Hospital, appreciate the implication of the disease duration as well as the type and the duration of treatment. It was found that hepatic and renal dysfunction were common in patients with typhoid fever. Typhoid fever induced hepatic damage at the first week of the disease resulting in significant variation of hepatotoxicity biomarkers independently of the type and drug intake duration. Concerning renal damage, it appears at the third week of typhoid fever and at two weeks of drug intake by a significant variation of nephrotoxicity biomarkers. Thus, the liver is always involved in typhoid fever but not kidney. However, treatment of typhoid fever with medicinal plants (indigenous) caused more hepatic and renal damage than treatment with fluoroquinolones.

6. Recommendations

Our results indicate that typhoid fever negatively affects the functioning of the liver or kidney with an implication of the disease duration the type and duration of treatment. Therefore, the following recommendations were made:

To the population:

- Get diagnosed when the first symptoms of the disease appear;

- Take conventional or herbal medicines under medical prescriptions.

To doctors:

- Take care of the liver and kidneys of people who have shown symptoms of typhoid fever for a long time or who have been on self-medication for a long time.

To the government:

- Promote awareness campaigns on the consequences of the long duration of the manifestation of typhoid fever and self-medication on the functioning of the liver and kidney of patients.

7. Data Availability

All data used or analyzed during this study are available from the corresponding author on reasonable request.

8. Conflicts of Interest

The authors declare no conflicts of interest.

9. Funding Statement

The authors declare that no funding was received for the study and all cost of the study was met through personal contributions.

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