

Full Length Research Paper

Association of metabolic syndrome with the risk of developing liver disease in chronic hepatitis B patients

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Metabolic syndrome is a constellation of abnormal glucose and lipid metabolic parameter that increases ones risk of developing cardiovascular diseases. Metabolic profiles have been linked to progression of varying stages of liver disease in chronic hepatitis B infection. The main objective of this prospective cross sectional study was to establish a link between metabolic syndrome indicators and markers of progression of liver disease in chronic hepatitis B infection. This could provide data leading to an alternative to managing the complications of chronic hepatitis B infection by possibly targeting metabolic precursors and their pathways which will be more targeting, sensitive and has minimal treatment complications than the conventional treatment regimes. In all, 200 chronic hepatitis B patients were sampled of which 100 met the United State National Cholesterol Education Program – Adult Treatment Panel III (US NCEP ATP III) 2005 criterion for metabolic syndrome. Anthropometric data and biochemistry analysis were performed. Obesity and dyslipidemia markers except HDL were higher in metabolic syndrome while haematological makers except WBC were lower in metabolic syndrome. Markers of liver carcinogenesis were generally higher in metabolic syndrome and strongly associated ($p=0.01$) with initial hepatocellular necrosis and cirrhosis stages of liver carcinogenesis than the intermediary fibrosis stages suggesting virologic mechanism may be responsible more for the fibrosis than metabolic factors. Metabolic syndrome was associated with the developing of various hepatitis B related liver complications. A long term study to elucidate viral genomic and dietary contributions to liver complications due to hepatitis B is necessary.

Key words: Metabolic syndrome, cardiovascular disease, carcinogenesis, anthropometry, chronic hepatitis, dyslipidemia, haematological, hepatocellular, fibrosis.

INTRODUCTION

The US NCEP-ATP III (2005) defines metabolic syndrome as the co-occurrence of any three of obesity, portal hypertension, atherogenic dyslipidemia, diabetes or impaired glucose utilization and microalbuminuria

(Chackrewarthy et al., 2013; Pedroza-Tobias et al., 2014). Metabolic syndrome indicates one's risk of developing cardiovascular diseases and dysregulation in the body's energy metabolism (Cheng et al., 2016).

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In 850 hepatitis B cohort, metabolic syndrome was found to be 5%, of which elevated fasting blood glucose (≥ 100 mg/dL) was most prevalent. The degree of liver fibrosis was higher in metabolic syndrome group. Higher body mass index (BMI), high aspartate transaminase (AST)/Alanine transaminase (ALT) and metabolic syndrome were correlated with advanced fibrosis ($p < 0.001$) (Aygün, 2015; Hsiang et al., 2014). In a long term population-based study, diabetes was correlated ($p < 0.01$) with advanced cirrhosis while extreme obesity (BMI ≥ 30 kg/m²) was 4 fold associated with liver cirrhosis, and 100 fold increase in risk of advanced liver cirrhosis and hepatocellular carcinoma when both diabetes and extreme obesity were present (Hoebel, 2010, Pathik et al., 2017).

Stages of liver disease in chronic hepatitis B infection

The hepatocyte necrosis stage or cell injury stage is the first phase of carcinogenesis. The infected hepatocytes display the viral surface antigens (HBsAg) and the core antigens (HBcAg) leading to activation of immune-mediated target cell lysis or necrosis (Liaw and Chang, 2014).

Fibrosis or the wound healing stage is the development of tough, fibrous scar tissues due to excessive accumulation of extra matrix protein such as collagen, laminin, elastin and fibronectin (Papastergiou et al., 2012; Howell et al., 2015). Prompt detection of hepatic fibrosis is essential to making therapeutic decisions, predicting clinical prognosis and future complications (Papastergiou et al., 2012; Castera, 2011). Patients with mild or absent fibrosis have 25 to 30% risk of developing cirrhosis in the next 20 years whereas patients with septal fibrosis develop cirrhosis in 8 to 10 years (Lee et al., 2016, El-Serag and Rodulf, 2007).

Advanced cirrhosis or hepatocellular carcinoma is characterized by massive morphological disruption of the liver architecture and aberration in liver hepatocyte regeneration mechanisms resulting in changes in hepatocytes nodules and vascular formations (Gristina et al., 2015).

Mechanism of effect of metabolic syndrome on development of liver disease

Metabolic syndrome is linked to liver carcinogenesis in chronic hepatitis B through insulin resistance, molecular regulation, generation of oxidative stress and host immunity suppression (Brian and Ma, 2012; Katoonizadeh et al., 2016).

Insulin resistance leads to accumulation of visceral fat which disrupt cortisol homeostasis resulting in a surge in adiponectin synthesis, reduced sero-clearance of triglycerides and Very-low-density lipoprotein (VLDL)

(Aygün, 2015; Mazzanti et al., 2016). These accumulatively generate insulin antagonist inflammatory cytokines such as tumor necrosis factor alpha, interleukin-6, insulin growth factor -1 (IGF-1) and resistin which initiate proliferation and antiapoptotic effect of hepatic stellate cells (Rahman et al., 2013; Jarcuska et al., 2016). Oncogenic mechanisms such as the C-Jun N-terminal Kinases (JNK) and nuclear factor Kb-1 (NF-kB-1) pathways that lead to hepatocellular carcinoma are activated by proinflammatory cytokines (Deng et al., 2015).

The NS3 and NS5 core proteins promote promitogenic in the hepatic stellate cells, stimulate the activation of NADPH oxidase and repress hemeoxygenase in hepatocytes further causing oxidative stress by accumulating lipid peroxides and free radicals (Svegliati-Baroni et al., 2014).

Immune response systems that produce multiple growth factors, inflammatory cytokines and chemostatins activate hepatic stellate cells, while those that generate kuffer cell-derived transforming growth factor and bile-induced activation of the epidermal growth factor promote hepatic stellate cells proliferation. Fibrogenic cytokine tumor growth factor B1 activates quiescent HSCs into contractile myoblast which eventually become a sustained source of extra metric proteins disrupting the extracellular matrix proteins turn over (Kuo et al., 2016; Rahman et al., 2013).

The surge in the prevalence of hepatitis B and metabolic syndrome, treatment cost and compliance challenges require early and comprehensive identification of persons at risk. The main objective of the study was to establish a link between metabolic syndrome indicators and markers of progression of liver complications in chronic hepatitis B infection. This could provide alternative to managing the disease by targeting metabolic precursors and their pathways.

MATERIALS AND METHODS

Ethical considerations and sample selection

Ethical approval was granted by the Committee on Human Research, Ethics, and Publication of the KATH and School of Medical Sciences, KNUST (CHRPE-SMS/KNUST-KATH). Subjects were selected from hepatitis B-infected patients attending clinical services at the Tamale Teaching Hospital. Inclusion into the study involved signing of an informed consent form by the volunteers and serological detection of HBsAg. Volunteers were recruited as they report to the Hospital.

Determination of sample size

In all, 200 chronic hepatitis B subjects were recruited using the population based formula by Krejcie and Morgan (1970). The formula takes into consideration the population of the study area, the prevalence of hepatitis B infection and 5% margin of error. Of this, 100 meet the US NCEP-ATP III (2005) criterion and were set as the test sample while 100 chronic hepatitis B patients which did not meet the US NCEP-ATP III (2005) criterion were set as control.

Recruits were excluded based on either one or more of evidence of smoking, use of drugs that affect the lipid profile, insulin administration, alcoholism, presence of liver complications and Hepatitis C virus (HCV) or have not met the US NCEP ATP III (2005) criteria.

Gathering of personal and anthropometry data

Data on age, gender, residency, marital status, level of education and presenting clinical symptoms were acquired using self-administered questionnaire. The body mass and height were measured with multipurpose stadiometer, Seca™ (Medical Measuring Systems and Scale, USA). The systolic and diastolic blood pressures were taken with sphygmomanometer, Baumanometer (Medical EXPO, UK). The waist circumferences were taken with a measuring tape KOMELON® (KOMELON Inc, USA). The BMI was calculated as body mass (kg) divided by the square of the height (m) (Sveglia-Baroni et al., 2014).

Biochemistry and haematological analysis

5.0 ml venous blood was drawn after 12-hour overnight fast using sterile syringes by phlebotomist into sterile vacutainers. About 2 ml of blood samples were collected into EDTA tube for haematological estimation while 3.0 ml was collected into dry tube for biochemical estimation. Glucose was estimated at the point of collection using glucometer (GLUCOCARD Expression, USA).

The viral serological test was performed using commercial Hepatitis B Virus profile test kit, Diaspot (Fortress Diagnostics Ltd., Antrim BT14 1QS, UK). The biochemistry analysis were performed using NADH oxidation-dependent spectrophotometric technique with commercial chemistry analyser Horiba (HORIBA medicals, France), while full blood count (FBS) was estimated using automated hematology analyzer, Humacount 30^{TS} (Human Diagnostic Worldwide, Germany).

Calculation of biochemical indices

The fibrosis-4-index (FIB-4) index and the aspartate to platelet ratio index (APRI) were calculated according to the formula by Van Der Meer et al. (2012) and Castera (2011) as follows:

$$APRI = \left(\frac{AST}{40} \right) \left(\frac{1}{PLATELETS(10^9/L)} \right) \times 100$$

$$\text{Fibrosis-4-index} = (\text{Age} \times \text{AST}) / (\text{Platelets} \times (\text{ALT})^2)$$

$$\text{Females: VAI} = \left(\frac{WC}{36.58 + (1.89 \times \text{BMI})} \right)$$

$$\times \left(\frac{TG}{0.81} \right) \times \left(\frac{1.52}{HDL} \right)$$

$$\text{Males: VAI} = \left(\frac{WC}{39.68 + (1.88 \times \text{BMI})} \right)$$

$$\times \left(\frac{TG}{1.03} \right) \times \left(\frac{1.31}{HDL} \right)$$

Where APRI is aspartate to platelet ratio index, AST is aspartate transaminase, HDL is High density lipoprotein, TG is triglycerides, and WC is waist circumference

Statistical analysis

Statistical analyses were performed with Minitab™ Version 16 (Minitab Inc, Pennsylvania, USA). Discrete data were reported as

percentages while continuous data were reported in mean and standard deviation. Correlation analyses were reported in p-values and correlation coefficient while regression analyses were reported in S-values, R-square and R-square adjusted.

RESULTS

Anthropometric, haematological and biochemical parameters of study population

Table 1 shows the anthropometric, haematological and biochemical parameters of the study population. Both groups had similar heights. Subjects with metabolic syndrome (MS) weighted 65.60±6.52 kg while the NMS group weighted 52.82±7.69 kg).

The BMI of MS category were in the obese category (>30 kg/m²) while that of the without MS (NMS) group was in overweight category (> 25 kg/m²). The waist circumference (WC) and visceral adiposity index (VAI) of MS group were 92.7±7.6 cm and 1.18±0.024, respectively whereas those in the NMS group were 85.11±8.13 cm and 0.42±0.25, respectively.

The lipid profiles also followed this trend, except for HDL cholesterol, where NMS group was 1.42±0.025 mmol/L while subjects with the syndrome was 1.28±0.61 mmol/L. Fasting blood glucose (FBG), coronary ratio and blood pressure of MS category were 8.24±2.16 mmol/L, 11.5±3.15% and 152/98±8.28 mmHg whereas NMS group were 6.19±2.98 mmol/L, 8.29±1.98% and 128/18.58 mmHg, respectively.

All the liver disease markers were generally higher in the MS category than NMS category, except for AST/ALT ratio where the MS group was lower (0.28±0.07) than the NMS group (0.78±0.29). For the haematological properties, the Hb and platelets counts were lower (11.6±4.21 g/dL and 218.61±97.41×10⁹/L, respectively) in the MS group compared to the NMS group (12.10±3.0g/dL and 258.63±108.19 g/dL, respectively). The WBC counts were slightly higher in the MS group than the NMS group (7.85±2.16×10⁹ and 7.29±1.20×10⁹/L, respectively). Regarding the number of subjects with results outside the reference limits, Body mass index (BMI), VAI, WC, VLDL, triglycerides, alanine aminotransferase (ALT), APRI and α-fetoprotein (AFP) of the MS group were generally higher than the NMS group except for fibrosis-4 index and haemoglobin counts, where the MS group were lower (14.7 and 28.14%, respectively) than the NMS group (32.16%).

Association of biochemical, viral serological and demographic parameters with metabolic syndrome

In MS group, AST/ALT was significantly correlated with BMI (p=0.12), FBG (p=0.024), Hepatitis B envelop antigen (HBeAg) seropositivity (p=0.01) and the total WBC count (p=0.027). The correlation with FBG and

Table 1. Anthropometric, haematological and biochemical features of study population stratified by the syndrome.

Marker	Metabolic syndrome (MS)		Without metabolic syndrome (NMS)		Total (Out of reference range)	p-Value
	Mean value	No. above reference limit n (%)	Mean value	No. above reference limit n (%)		
Anthropometries						
Height (m)	1.62±0.43		1.61±0.78		0.779	
Weight (kg)	65.6±6.52		52.8±7.69		0.769	
BMI (kg/m ²)	35.7±3.25	42 (21)	27.01±4.72	26 (13.0)	68 (34.0)	0.113
WC (cm)	92.7±7.62	9 (4.5)	85.11±8.13	5 (2.0)	14 (7.5)	0.000
VAI	1.18±0.02	48 (24)	0.42±0.25	29 (14.5)	77 (38.5)	0.012
Lipid profile/CVD						
HDL-CHOL	1.28±0.61	25 (12)	1.42±0.025	12 (6.0)	37 (16.5)	0.931
LDL (mmol/L)	4.93±0.78	32 (16)	4.31±0.98	23 (11.5)	55 (27.5)	0.031
TRI (mmol/L)	1.73±0.65	45 (22.5)	1.42±0.05	20 (10)	65 (32.5)	0.949
TCHOL(mmol/L)	7.93±2.98	20 (10.0)	5.92±0.97	11 (5.5)	33 (16.5)	0.736
VLDL (mmol/L)	1.91±0.30	35 (17.5)	0.96±0.19	32 (16.0)	67 (33.5)	0.000
FBG (mmol/L)	8.24±2.16	28 (14)	6.19±2.98	13 (6.5)	41 (20.1)	0.941
CR (%)	11.5±3.15	8 (4.0)	8.29±1.98	1 (0.05)	9 (4.5)	0.885
BP (mmHg)	152/98±8.28	35 (17)	128/70±8.5	32 (16.0)	67 (33.5)	0.945
HBeAg RR	14(7.0)	2 (1.0)			8 (4.0)	0.021
Liver disease						
AST/ALT	0.28±0.07	31 (15.5)	0.78±0.29	30 (15%)	61 (30.5)	0.513
APRI	0.64±0.13	24 (12)	0.41±0.18	12 (6%)	36 (18.0)	0.000
AFP (µg/L)	3.73±2.12	12 (6.0)	2.67±1.20	10 (5%)	22 (11.0)	0.000
FIB-4	0.90±0.69	14 (7.0)	0.80±0.21	32 (16.0%)	46 (23.0)	0.000
Haematology parameters						
Hb (g/dL)	11.6±4.21	28 (14)	12.10±3.20	32 (16.0%)	60 (30.0)	0.718
T.WBC	7.85±2.16	32 (16)	7.29±1.20	20 (10.0%)	58 (29.0)	0.512
Platelets	218.61±9	23 (11)	258.63±108.1	18 (9.0)	41 (20.5)	0.012

APRI, Aspartate to platelet ratio index; T.WBC, Total white blood cells; FIB-4, Fibrosis-4 index; CR, Coronary ratio; AFP, Alpha fetoprotein.

HBeAg seropositivity was stronger (co-efficient of 0.86 and 0.84, respectively) than BMI and WBC (co-efficient of 0.26 and 0.36, respectively). For the NMS group, AST/ALT ratio only correlated significantly with FBG and HBeAg seropositivity ($p=0.02$ and 0.024 , respectively) (Table 2).

APRI also correlated significantly with BMI ($p=0.021$) only in the MS group and no parameter in NMS group. Similarly, FIB-4, correlated with only HBeAg seropositivity in both categories ($p=0.032$ and 0.024 , respectively). AFP also correlated with VLDL, VAI and HBeAg seropositivity ($p=0.040$, 0.024 and 0.01 , respectively) in the MS group and with only FBG ($p=0.03$) in the NMS category.

HBeAg seropositivity correlated with only VLDL in both categories ($p=0.040$ and 0.032 , respectively) while CR correlated with VAI, VLDL and triglycerides ($p=0.02$, 0.032 and 0.03 respectively) in subjects with the MS.

Correlation of metabolic syndrome with hepatitis B related liver disease

Table 3 shows the correlation of MS and NMS groups with liver disease markers. MS category generally correlated with AFP, AST/ALT ratio, APRI and CR levels. The correlation varied with CR being the strongest, followed by AFP, AST/ALT ratio and APRI with p-values indicated in their category in Table 3. Subjects that did meet the criteria for metabolic syndrome correlated with FIB-4 ($p=0.049$) and CR ($p=0.029$).

CR was more associated with the MS markers (Table 4) having the lowest S-value but the highest R-square and R-square adjusted values as indicated in Table 4. Necrotic markers, AST/ALT and APRI, had similar strength of association of their respective related variables as shown. FIB-4 was weakly associated with MS markers having the highest S-value and lower R-

Table 2. Association of biochemical, viral serological and demographic parameters with metabolic syndrome.

Parameter	Metabolic syndrome	Without metabolic syndrome
AST/ALT	BMI-0.26 (0.012)	FBG-0.213 (0.02)
	FBG-0.86 (0.024)	HBeAg RR-0.18 (0.024)
	HBeAg-RR-0.84 (0.01)	
	WBC-0.36 (0.027)	
APRI	BMI-0.26 (0.021)	None
FIB-4	HBeAg RR-0.86 (0.032)	HBeAg RR-0.86 (0.024)
AFP	VLDL-0.58 (0.040)	FBG-0.23 (0.03)
	VAI-0.68 (0.024)	
	HBeAg RR-0.184 (0.01)	
HBeAg seropositivity	VLDL-0.58 (0.040)	VLDL-0.58 (0.032)
	VAI-0.92 (0.02)	
	VLDL-0.58 (0.032)	None
	TRI-0.84 (0.03)	

Values are represented as correlation coefficient in brackets the corresponding p-value. APRI, Aspartate to platelet ratio index; T.WBC, Total white blood cells; FIB-4, Fibrosis-4 index; CR, Coronary ratio; AFP, Alpha fetoprotein.

Table 3. Correlation of metabolic syndrome with Hepatitis b related liver disease.

Category	Total n(%)	Female n (%)	Male n (%)	Liver markers disease	p-value
With metabolic syndrome	100 (50.0)	62 (31.1)	38 (18.0)	AFP	0.01
				AST/ALT	0.01
				APRI	0.017
				CR	0.003
Without metabolic syndrome	100 (50.0)	49 (24.5)	51 (25.5)	FIB-4	0.049
				CR	0.029

Table 4. Extent of association of metabolic syndrome with liver diseases.

Liver disease marker	S-value	R ² -value (%)	R ² (adjusted value) (%)
Metabolic syndrome group			
Hepatocellular necrosis			
AST/ALT ratio	0.61	10	5.8
APRI	0.62	11.9	6.8
Liver fibrosis			
FIB-4	2.11	6.1	0.6
Liver cirrhosis/HCC			
AFP	234.44	5	5
Cardiovascular disease risk			
CR	1.03	67.4	65.5
Non-metabolic syndrome group (Control)			
FIB-4	1.31	49.5	58.7
CR	3.3	63.7	52.7

square and R-square adjusted values as shown in Table 4. Generally the studied metabolic syndrome markers correlated with their liver disease markers in decrease strength from CR, APRI, AST/ALT ratio, AFP and FIB-4 using the indices shown in Table 4.

DISCUSSION

Subjects with abnormal levels of the studied liver and cardiovascular disease markers were higher in the metabolic syndrome category than NMS category except FIB-4. FIB-4 indicates the risk of hepatic fibrosis and poor extra-matrix protein turn over (Kasmari et al., 2017). FIB-4 correlated significantly with HBeAg seropositivity in both categories ($p=0.032$ and 0.024 , respectively). FIB-4 was also strongly associated with the absence of metabolic syndrome than its presence ($s=1.31$, $R=49.5\%$, $R^2=58.7\%$ and $s=2.11$, $R=6.1\%$, $R^2=0.6\%$) respectively. HBeAg seropositivity is an indication of high viremia, high rate of replication or infectivity and an immune escaping genotype (Kasmari et al., 2017). These suggest that, though metabolic syndrome poses risk to the development of liver and cardiovascular diseases, viral load and genotype contribute significantly to the development of hepatic fibrogenesis.

The necrosis stage of hepatic complication relies on host immune capacity to destroy HBsAg antigen displaying hepatocytes, minimize immune evasion and inhibit the c-Jun N-terminal kinase (JNK) pathway from initiating hepatic stellate cells synthesis. The fibrosis stage rather relies on microinflammation to initiate the JNK pathway and accumulate matrix protein (Dragut et al., 2016).

Alteration in AST/ALT ratio and APRI are markers of hepatocytes necrosis resulting from the viral infection, FIB-4 for the extent of fibrosis and AFP indicates the presence of substantial cirrhosis and hepatocellular carcinoma (Kaur, 2014, Boyd et al., 2017). AST/ALT ratio correlated significantly with BMI ($p=0.012$), fasting blood glucose ($p=0.024$) and HBeAg ($p=0.01$). APRI correlated significantly with BMI ($p=0.021$); AFP correlated significantly with FBG and VLDL ($p=0.03$ and 0.04) respectively while HBeAg significantly correlated with VLDL ($p=0.040$). Metabolic syndrome is a constellation of signs of both extra and intracellular energy metabolism disorder and the more the markers present, the higher the risk of development of the liver or cardiovascular diseases (Maud et al., 2017). These however suggest that all the risk factors do not contribute and if at all not equally to the development of the stages of liver disease. Further, high BMI, FBG and VLDL may contribute greatly to the development of liver disease than the other risk factors.

Metabolic syndrome influences the development of hepatic steatosis by fluxing the circulatory system with VLDL and small dense (sd)-LDL, generation of reactive oxygen species and induction of non-alcoholic fatty liver

(Sugihara et al., 2016). VLDL and sd-LDL are precursors for the packaging of the viral outer protein coat, which is required for the virulence and replication of the virus (Li and Zhao, 2017). Fatty liver is also associated with lipotoxicity and generation of reactive oxygen species which is toxic to the membranes of the infected hepatocytes. Diabetes or impaired glucose utilization and visceral obesity are also associated with generation low grade inflammatory cytokines and tumor necrosis factor-1 which are essential initiators of the JNK pathway for the initiation of the hepatic stellate cells synthesis (Maud et al., 2017).

These outcomes agrees with Nau et al. (2014), where metabolic syndrome was significantly associated with the necrosis, fibrosis and cirrhosis stage of liver disease development ($p=0.01$). HBeAg seropositivity had positive significant correlation with AFP ($p=0.01$). HBeAg seropositivity indicates high infectivity or active replication suggesting the essence of virologic factors in the expansion of the hepatic stellate cells, extra matrix protein turn over disruption and subsequent morphological deformation of the liver. It further confirms the importance of metabolic precursors such as VLDL in the packaging of the outer protein coat of the virus which favor the development of hepatocellular carcinoma, cirrhosis and hepatoma (Changotra et al., 2008).

A study by Hsiang et al. (2014) confirmed that metabolic syndrome delays serum disappearance HBeAg positive cohorts by 18.9% ($p=0.001$). Metabolic syndrome was also used as baseline predictor of delayed HBeAg seroclearance when adjusted for viral load and antiretroviral therapy (Hsiang et al., 2014).

VLDL was associated with presence of HBeAg irrespective of the presence or absence of metabolic syndrome. VAI identified more obese and overweight persons than the anthropometric obesity markers waist circumference and BMI. Metabolic syndrome is a factor of genetic, dietary and environmental disposition; it is therefore recommended that a follow up study on the role of genotypes, viral load and dietary roll call on the development of these liver conditions.

Metabolic syndrome was associated with the hepatocyte necrosis stage and development of hepatocellular carcinoma or cirrhosis stages, however viral load and genotype contribute significantly to the development of hepatic fibrosis.

Limitations of the study

The study did not take into consideration the role of the different genotypes of the hepatitis B virus as well as the viral loads which are also determinants of the clinical outcomes of the infection.

CONFLICTS OF INTERESTS

The authors have not declared any conflict of interests.

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