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Role of Emerging Risk Markers in Cardiometabolic Syndrome

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Abstract: Cardiometabolic syndrome (CMS), also known as metabolic syndrome (MetS) is a common and silent epidemic, which is linked to type 2 diabetes mellitus, abdominal obesity, and a higher risk of cardiovascular disease. Comprehensive demographic, physiological, genetic, and clinical data were collected from 199 subjects suffering from varying degrees of Metabolic syndrome (MetS) and 100 healthy control subjects. Mutagen induced chromosome sensitivity analysis for DNA repair proficiency and the extent of somatic DNA damages by Cytokinesis-Block Micronuclei (CBMN) assay were also performed among the study subjects. The study found that individuals with CMS showed an elevated concentration of Lp-PLA2, MA and hsCRP. The study also showed an association between DNA damage and DNA repair among the test subjects. Microalbumin and Lp-PLA2 can be considered good markers for the early prediction of coronary artery disease (CAD) and several other cardiovascular diseases. In addition, the rising frequency of somatic DNA damage points to the varied degrees of MetS progression. Thus, novel biomarkers can identify patients who are at risk beyond traditional ones, thereby alleviating the possible CMS events and also other disorders related to CMS by following healthy lifestyle habits and proper medication.
Keywords: Cardiometabolic syndrome, Risk markers, Coronary Artery Disease, Lp-PLA2, hsCRP, Microalbuminuria, DNA repair mechanism, Somatic DNA damages

Introduction

Cardiometabolic syndrome (CMS) is a complex cluster of risk factors for cardiovascular disease (CVD) and diabetes as defined by Alberti et al. (2009). Isomaa et al. (2001) reported that “the risk of coronary heart disease (CHD), myocardial infarction, and stroke is much higher in persons who have the cardiometabolic syndrome than in those

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without the syndrome". Babu & Fogelfeld (2006) suggested that "CMS is a prediabetic state" and CMS was first mentioned by Gerald Reaven as Syndrome X or the Insulin Resistance Syndrome (Reaven, 1998). The cardiometabolic syndrome is also known as insulin resistance syndrome because Reaven (1988) has hypothesized that insulin resistance is the major mechanism responsible for the metabolic abnormalities of the syndrome.

No universally accepted definition of the CMS has been established, and at least 5 independent groups have proposed clinical criteria for establishing its diagnosis (Grundy et al., 2005). According to Grundy et al. (2005), CMS can be diagnosed if, at least three out of the following five criteria is confirmed: abdominal obesity, elevated TG level, reduced high density lipoprotein (HDL), hypertension, and disturbances in fasting glucose. Paschos & Paletas (2009) estimated that over 23% of the general population suffers from CMS, and 10% of these patients demonstrate the presence of all five criteria.

CMS is believed to affect at least one in five adults worldwide and carries a high risk of CVD (Magliano et al., 2006). The prevalence of CMS in the studies ranged from 6.3% among apparently healthy populations (Siminialayi et al., 2008). According to the National Cholesterol Education Program (US) (2002), the latest National Health and Nutrition Examination Survey (NHANES) data found that the prevalence of CMS is increasing in both men and women in all age groups. Mean prevalence of CMS over the 12 years for hospital-based studies was 41.8% (World Health Organisation [WHO]), 38.4% Third Adult Treatment Panel (ATP III) and 40.8% International Diabetes Federation (IDF) (Oguoma et al., 2015).

The CMS has become a major public health problem in the United States and many other countries worldwide because of its increasing prevalence (Kirk & Klein, 2009). Moreover, Yoon et al (2015) mentioned that "metabolic syndrome (MetS) has been associated with increased risks of developing diabetes mellitus and CVD as well as increased mortality". Emerging risk markers such as Lipoprotein-associated phospholipase A2 (Lp-PLA2), high sensitivity C-reactive protein (hsCRP), microalbumin (MA), and the extent of somatic DNA damage are vital to providing specific value when compared to the traditional markers.

Lipoprotein-Associated Phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2) has emerged recently as an independent, inflammatory marker of cardiovascular (CV) risk and events (Häkkinen et al., 1999). Several epidemiologic studies have investigated the association between plasma Lp-PLA2 concentration and risk for subsequent CV events. Moreover, Tellis & Tselepis (2009) added that Lp-PLA2 is a calcium-independent phospholipase produced by hematopoietic cells and is mostly bound to lipoproteins in the plasma. Koenig et al., (2006) reported that Lp-PLA2 has been shown to predict future CV events in patients with coronary artery disease (CAD) independently of traditional risk markers and markers of inflammation, haemodynamic stress and renal function. Lp-PLA2 was shown to be associated with long-term cardiac and total mortality adjusted for established risk factors including NT-pro-BNP, hsCRP and even angiographically determined CAD status (Winkler et al., 2007).

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High sensitivity C-reactive protein

In a study done by Denegri & Boriani (2021), high sensitivity C-reactive protein (hsCRP) is a well-established marker of CV disease; high levels of hsCRP have been associated with adverse CV outcomes after acute coronary syndrome (ACS). Shih et al. (2022) pointed out that hsCRP is elevated in inflammatory situations, and can be produced by monocyte-derived macrophages in adipose tissue. Torres & Ridker (2003) described that increased levels of high sensitivity CRP (hsCRP) may be used as a tool to facilitate the diagnosis, prevention and treatment of CVDs. Haddy et al. (2003) noted that "hsCRP is one of the most powerful markers for predicting Coronary Heart Disease (CHD)". Parrinello et al. (2015) observed that, "sustained elevations in hs-CRP over 6 years were associated with a subsequent increased risk of diabetes, and persons with sustained elevations in hsCRP were at the highest risk for cardiovascular disease and mortality". Shrivastava et al. (2015) explained that, "the availability of hsCRP assays has supported CRP as a strong biomarker in clinical practice because of its long half-life, stability, ease of assay and reproducible results".

Microalbuminuria

Heerspink et al. (2008) defined Microalbuminuria as urinary albumin excretion of 20-200 mg/L, which is an early marker of chronic kidney disease (CKD) and Sheng et al. (2011) found out that it is also associated with an increased risk of cardiovascular disease, all-cause mortality, and metabolic disorders, including type 2 diabetes mellitus (T2DM) and MetS. Danziger (2008) also stated that "microalbuminuria is associated with salt sensitivity and hypertension, obesity, insulin resistance and diabetes as well as other components of the MetS such as dyslipidemia". Ninomiya et al. (2009) points out that, "microalbuminuria and low estimated glomerular filtration rate (eGFR) have been shown to be associated with adverse cardiovascular and renal outcomes independent of cardiovascular risk factors". Schachinger et al. (2000) described that, "as there is no plausible mechanism directly linking atherothrombotic disease to the urinary albumin loss, endothelial dysfunction has been suggested to be, at least partly, the pathophysiological process that causes both increased renal albumin loss and coronary artery disease endothelial dysfunction, which occurs early in the atherosclerotic process".

DNA Repair Mechanism

Prates Mori & de Souza-Pinto (2018) described that "DNA is constantly being damaged, either by endogenous or exogenous genotoxins. DNA repair activities are essential for maintaining genomic stability and to life itself". Tekeli et al. (2008) pointed out that, "genetic variations in DNA repair genes can modulate DNA repair capacity and consequently, alter CAD risk". Bazo et al. (2011) concluded that "individuals with the variant XRCC1 (X-ray cross-complementing group 1) DNA repair genotype had a 2.3-fold increased risk for coronary atherosclerosis than individuals with the wild-type genotype". Wang et al. (2010) explained that, "in atherosclerotic plaques, there is evidence of activation of DNA repair mechanisms along with signs of DNA damage, base excision repair, and mismatch repair, whereas patients with specific polymorphisms in genes responsible for DNA repair

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have been found to be more susceptible to CAD". Simon et al. (2013) explained that, "malondialdehyde (MDA), which is an indicator of oxidative stress, and mean break per cell (b/c) values, which is an indicator of decreased DNA repair efficiency, were found to be significantly increased in CAD patients compared to normal controls".

Somatic DNA Damages

Bazo et al. (2011) revealed that "the increased levels of DNA damage induced by xenobiotics play an important role in the early phases of atherogenesis". Priya et al. (2008) noted that "lipid peroxidation, which is mediated by free radicals, is considered to be the major mechanism of cell membrane destruction and cell damage". Mahmoudi et al. (2008) reported that "DNA damage is seen in early atherosclerotic lesions and becomes almost universal in advanced plaques". Another study by Mahmoudi et al. (2006) revealed that the "major cause of DNA damage in atherosclerosis is oxidative stress". Andreassi et al. (2009) expressed that, "the increase in DNA damage depends on the severity of atherosclerotic disease in patients with CAD". Federici et al. (2008) described that "somatic deoxyribonucleic acid (DNA) damage has been associated with early-phase or acute complications of atherosclerosis". Gallagher et al. (2010) showed that "Increased oxidative stress in obesity and metabolic syndrome has been linked with DNA damage and subsequent malignancies". Al-Aubaidy & Jelinek (2011) identified that "DNA damage can alter regulation of cell cycle along with other cellular processes including transcription, signal transduction pathways, replication mismatch, DNA damage repair and resultant genomic instability, which may eventually lead to tumorigenesis".

Most of the previous studies in CAD associated with MetS were conducted either on biochemical risk factors or genetic damages. Very few attempts were made to evaluate the role of emerging risk markers like Lp-PLA2, hsCRP, microalbumin, DNA repair proficiency and somatic DNA damage associated with CMS. Hence the study evaluates the role of various novel biomarkers in association with CMS and correlates the changes with the syndrome. Moreover, the study describes the current advances in the assessment of metabolic risk and the personalization of the clinical management of the disease thereby preventing future risks for cardiovascular diseases. The aim of the present study is to evaluate and compare the role of various emerging risk markers like Lp-PLA2, hsCRP, microalbumin, DNA repair mechanism and somatic DNA damages among the subjects with varying degrees of cardiometabolic syndrome.

Materials & Methods

The present study was conducted on 299 subjects. Among them, 199 test subjects were suffering from varying degrees of cardiometabolic syndrome and 100 healthy subjects were selected as the control for this study. Detailed demographic, physiological, genetic and clinical characteristics were recorded using proforma after getting informed consent from patients. Eight ml of venous blood was collected aseptically from all the subjects by venipuncture after overnight fasting. Three ml of blood was collected in a sodium heparinized vacutainer for quantifying the extent of somatic DNA damage by Cytokinesis-block

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micronuclei (CBMN) assay and the evaluation of DNA repair proficiency by mutagen induced chromosomal sensitivity analysis. The remaining 5 ml blood was collected and serum was separated for the biochemical analysis such as Total cholesterol (TC), High density lipoprotein (HDL), Low density lipoprotein (LDL), Triglycerides (TG) and hsCRP Lp-PLA2 activity level is measured using spectophotmetric method in nmol/min/mL. About 10 mL of Random Urine was collected and urine microalbumin and creatinine were analysed to calculate the microalbuminuria (MA).

Observation & Results

The age of the study subjects ranged from 40 to 60 years with a mean age of 57.46 ± 7.751 for test subjects and 57.19 ± 8.027 for the control. No statistical significance difference between the mean age of test and control subjects was observed (t= -0.28 and p= 0.781). The age range of the test subjects was categorized into two groups (≤50 and >50 years). Test subjects in the age group >50 yrs (n=164) showed elevated MA value, Lp-PLA2 concentration, mCBMNF and mean b/c value. The male test subjects (n=112) showed increased MA and hsCRP than the female test subjects. While Lp-PLA2 and mean CBMN frequency (mCBMNF) values were comparatively high in female test subjects (n=87). The test subjects were classified based on their area of residence as coastal, rural and urban. Those who reside in urban areas (n=91) showed an increased mean CBMN frequency (12.7) and microalbuminuria than the rest. The highest value of Lp-PLA2 was observed in subjects living in the coastal area. Test subjects with a sedentary type of occupation (n=27) showed increased value in all tested biomarkers (MA, hsCRP, Lp-PLA2), mCBMNF and mean b/c value (Table 1).

Variables	**Category**	**No.**	**MA** (mg/g Cr)	**hsCRP** (mg/L)	**Lp-PLA2** (nmol/min/mL)	**Mean CBMN frequency**	**Mean b/c value**
Age (Years**)**	≤50	35	276	3.5	281	12.5	0.870
	>50	164	283	3.5	282	12.6	0.872
Gender	Female	87	273	3.4	286	12.5	0.88
	Male	112	288	3.5	278	12.6	0.865
Residence	Urban	91	291	3.5	281	12.7	0.876
	Rural	87	276	3.5	279	12.6	0.868
	Coastal	21	271	3.4	290	12.5	0.869
Type of occupation	Sedentary	27	283	3.7	282	12.6	0.872
	Non-sedentary	172	282	3.4	279	12.48	0.871

Table 1: Comparison of emerging risk markers based on demographic characteristics

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Variables	**Category**	**No.**	**MA** (mg/g Cr)	**hsCRP** (mg/L)	**Lp-PLA2** (nmol/min/ mL)	**mCBMNF**	**Mean b/c value**
Waist circumference (cm)	50 - 75	23	267	3.7	295	12.6	0.876
	76 - 100	105	282	3.5	279	12.5	0.873
	101 - 136	71	286	3.3	280	12.6	0.868
BMI (Kg/m^2**)**	≤25	46	280	3.4	280	12.1	0.870
	>25	153	288	3.5	285	12.7	0.878

Table 2: Comparison of emerging risk markers based on physiological characteristics

The waist circumference of the test subjects was grouped into 50 – 75cm, 76 -100 cm and 101 – 136cm. An increased level of MA was observed in subject group 101 – 136cm (n=71). Elevated hsCRP, Lp-PLA2, mCBMNF and mean b/c value were observed in the subject group 50-75cm. Out of 199 test subjects, 153 subjects showed BMI >25 Kg/m^2 and 46 subjects showed BMI ≤25 Kg/m^2. Subjects with greater BMI values showed high MA value, hsCRP level and elevated Lp-PLA2 concentration. Increased somatic DNA damage was also observed in these subjects (Table 2).

Variables	**Category**	**No.**	**MA** (mg/g Cr)	**hsCRP** (mg/L)	**Lp-PLA2** (nmol/min/mL)	**mCBMNF**	**Mean b/c value**
H/o HT	Yes	92	292	3.5	283	12.72	0.878
	No	107	273	3.4	281	12.02	0.865
H/o DM	Yes	84	299	3.5	268	12.58	0.871
	No	115	269	3.4	291	12.02	0.872
H/o Bacterial Infection	Yes	10	283	3.5	283	12.6	0.873
	No	189	266	3.2	250	12.1	0.842
H/o Dyslipidemia	Yes	110	285	3.6	282	12.6	0.873
	No	89	280	3.1	281	12.5	0.870

Table 3: Comparison of emerging risk markers based on biochemical characteristics

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Variables	**Category**	**No.**	**MA** (mg/g Cr)	**hsCRP** (mg/L)	**Lp-PLA2** (nmol/min/mL)	**mCBMNF**	**Mean b/c value**
Habit of Smoking	Yes	38	289	3.52	283	12.48	0.873
	No	161	253	3.14	277	12.04	0.866
Habit of Chewing	Yes	18	288	3.8	291	12.71	0.874
	No	181	281	3.67	281	12.2	0.870
Alcohol consumption	Yes	44	285	3.48	287	12.6	0.877
	No	155	261	3.1	280	12.08	0.861
Dietary Pattern	Non-veg	183	284	3.4	280	12.6	0.871
	Veg	16	262	3.7	298	12.5	0.879

Table 4: Comparison of emerging risk markers based on lifestyle parameters

The test subjects with H/o Hypertension (n=92) showed increased MA, hsCRP, Lp-PLA2, mCBMNF and mean b/c value. Out of 199 test subjects 84 subjects showed H/o Diabetics Mellitus (DM) and they showed increased MA and hsCRP. Test subjects without the H/o DM (n=115) showed increased Lp-PLA2 and mean b/c value. H/o Bacterial infection was observed only in 10 test subjects, and they showed increased MA value, hsCRP and Lp-PLA2 concentration than test subjects without H/o bacterial infections. Among 199 test subjects, 110 subjects showed H/o dyslipidemia with elevated levels of risk markers (Table 3).

Test subjects with the habit of smoking, alcohol consumption and habit of chewing showed an elevated MA value, mCBMNF, increased mean b/c value, increased hsCRP concentration and high Lp-PLA2 level.

When it comes to dietary patterns, non-vegetarian test subjects showed high MA values and elevated mCBMNF. Whereas, test subjects with vegetarian dietary patterns showed high hsCRP concentration, elevated Lp-PLA2 level and increased mean b/c value (Table 4).

Variables	**Category**	**No.**	**MA** (mg/g Cr)	**hsCRP** (mg/L)	**Lp-PLA2** (nmol/min/mL)	**mCBMNF**	**Mean b/c value**
Total Cholesterol (mg/dL)	≤200	113	267	3.2	280	12.4	0.866
	>200	86	293	3.8	284	12.7	0.876
HDL-C	≤40	127	289	3.6	293	12.78	0.872

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(mg/dL)	>40	72	280	3.4	271	12.02	0.870
LDL-C (mg/dL)	≤100	51	280	3.3	278	11.85	0.868
	>100	148	287	3.5	293	12.77	0.882
TG (mg/dL)	≤150	116	270	3.4	266	12.04	0.864
	>150	83	289	3.5	293	12.68	0.877

Table 5: Comparison of emerging risk markers based on lipid profile

Test subjects with TC level >200 mg/dL showed an increased MA value, high hsCRP, elevated Lp-PLA2, increased mCBMNF and mean b/c value when compared to the rest with total cholesterol level ≤200 mg/dL. Similarly, test subjects with an increased level of LDL-C (>100 mg/dL) and TG (>150 mg/dL) showed an elevated level of emerging risk markers. In the case of HDL-C level, test subjects with HDL-C ≤40 mg/dL showed high MA value, hsCRP level, Lp-PLA2 concentration, elevated mCBMNF and mean b/c value (Table 5).

Variables	**Category**	**No.**	**MA** (mg/g Cr)	**hsCRP** (mg/L)	**Lp-PLA2** (nmol/min/mL)	**mCBMNF**	**Mean b/c value**
HbA1c (%)	≤6	82	272	3.2	279	12.6	0.866
	>6	117	289	3.6	284	12.6	0.875

Table 6: Comparison of emerging risk markers based on HbA1c level

Out of 199 test subjects, 82 were reported with HbA1c level ≤6% and the remaining 117 with HbA1c levels >6%. Test subjects with HbA1c level >6% showed an elevated level of risk markers (Table 6).

Discussion

According to Aljohani (2014), metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors that include hyperglycemia, hypertension, obesity and dyslipidemia that increase the risk of diabetes mellitus type II and cardiovascular diseases. In the present study, 199 test subjects suffering from varying degrees of the cardiometabolic syndrome and 100 healthy control subjects were selected.

In the current study, elevated Lp-PLA2 and MA values were observed among the test subjects as age advances and those with the habit of smoking. Tsimikas et al. (2009) identified that “increased Lp-PLA2 activity is associated with MetS and incidence of fatal and nonfatal CVD. Furthermore, an insignificantly higher level of Lp-PLA2 was found in the patients with MetS compared to the patients without MetS”. In a study done by Elkind et al. (2009), a strong association was seen in MetS between the two inflammatory markers, Lp-PLA2 and hsCRP levels.

Hatoum et al. (2010) studied patients between 50 and 60 years old and observed that the Lp-PLA2 enzyme was modestly associated with total cholesterol, LDL-C, Apo B and

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BMI; however, the lipid adjustment attenuates the relation between BMI and Lp-PLA2. Manafa et al. (2019) also mentioned that "the increased level of Lp-PLA2 along with its positive correlation with other traditional markers like age and smoking duration suggests that Lp-PLA2 is a suitable biomarker to predict cardiac related diseases among cigarette smokers".

In the current study, test subjects reported with a sedentary type of occupation showed an increased level of MA value, high hsCRP level and an elevated Lp-PLA2 concentration when compared to the rest. Kivimaki et al. (2013) found the "risk among participants who had job strain compared with those who had no job strain". In the present study, people who reside in urban areas showed an increased value of hsCRP, mean CBMNF and MA. Moreover, Acevedo et al. (2009) mentioned that "the hsCRP is elevated in an urban population of Santiago, Chile, with metabolic syndrome (MetS), and there is a clear correlation between MS, hsCRP, and subclinical atherosclerosis in this population".

In this study, test subjects reported with a vegetarian diet showed an increased level of hsCRP and Lp-PLA2 concentration. Whereas, non-vegetarian test subjects showed high MA value and elevated mCBMNF. Likewise, Chrysohoou et al. (2004) indicated that "adherence to the traditional Mediterranean diet was associated with a reduction in the concentrations of inflammation markers and this has a beneficial effect on the cardiovascular system".

In the current study, there was an elevated MA value associated with those who have the habit of smoking and with a history of dyslipidemia and diabetes mellitus. Cirillo et al. (2005) stated that "hypercholesterolemia, smoking and diabetes mellitus were associated with a high prevalence of microalbuminuria independently of blood pressure and of each other, thus the prevalence of microalbuminuria was progressively higher with increasing the number of the individual's CMS thereby alleviating cardiovascular risk factors".

The present study observed that, subjects with high waist circumference showed an elevated hsCRP concentration. Accordingly, in a study done by Koziarska-Rościszewska et al. (2021), the concentration of hsCRP significantly correlated with BMI value; the concentration of hsCRP increased with the increase in BMI. According to Walvekarl et al. (2015), "anthropometric parameters such as Body Mass Index (BMI), Waist Circumference (WC) are widely used for the measurement of visceral adiposity. Both the parameters help to identify the subjects with CMS easily".

In the current study, it was mentioned that subjects with high waist circumference also showed an increased hsCRP value. This is in agreement with the study of Koziarska-Rościszewska et al. (2021) that the level of hsCRP increased with increasing waist circumference. In the present study, the subjects who were hypertensive showed an elevated hsCRP value. Koziarska-Rościszewska et al. (2021) noted that "hsCRP levels were also significantly higher in subgroups of the patients suffering from CVD, hypertension, diabetes, and visceral obesity compared to subgroups of subjects without such disorders".

The current study showed an increased incidence of MA was shown by subjects having >6% HbA1c value. Similarly, few studies have investigated the association between microalbuminuria and surrogate marker of insulin resistance such as hemoglobin A1c (HbA1c), TG/high-density lipoprotein cholesterol (HDL-C) ratio and serum alanine

transaminase (ALT) in the pediatric population (Huang et al., 2015), which have been widely accepted as risk factors of microalbuminuria in adults. Moreover, Cho & Kim (2017) also observed that microalbuminuria was associated with the level of HbA1c in both the obese and non-obese groups.

Conclusion

Metabolic syndrome is a cluster of cardiometabolic risk factors that includes insulin resistance, abdominal obesity, hypertension and dyslipidemia. MetS increases the risk of type 2 diabetes mellitus, cardiovascular diseases and all-cause mortality. A rising incidence of risk factors linked to a variety of lifestyle choices has led to a rise in the burden of MetS in India. For the early diagnosis of CAD and other CVDs, several conventional markers were employed, but it was also necessary to incorporate new risk markers. In the current study, the role of several emerging risk markers like Lp-PLA2, hsCRP, microalbumin, DNA repair mechanism and somatic DNA damages was analyzed among the subjects with varying degrees of cardiometabolic syndrome. Accordingly, when compared to conventional risk indicators, developing risk markers including Lp-PLA2, hsCRP, and MA offer particular diagnostic and prognostic values. Thus, it is best to prevent an increase in DNA damage, Lp-PLA2, hsCRP, and MA, which causes cardiovascular diseases. Certain dietary adjustments, lifestyle changes, and the implementation of the right medications can lower the chance of developing CMS as well as other disease conditions in relation to this.

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