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Inflammatory biomarkers have been inadequate in predicting heart attacks and strokes. Many of these markers also lack specificity as they are affected by multiple factors. Science is still evolving as the relationship between chronic inflammation and atherosclerosis has only been discovered and studied in recent decades, and so these inflammatory markers are continuing to be identified and developed. There is a growing panel of indicators for cardiovascular disease (CVD) and risk, and the newer markers are filling the need to test for more precise pathological conditions.

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) is a newer, vascular-specific inflammatory marker that has been shown to distinguish rupture-prone plaque. It is a unique phospholipase A$_2$ enzyme produced in the plaque of inflamed arterial walls predominantly by macrophages, but also other inflammatory cells. It binds with lipoproteins, mostly low-density, and it initiates hydrolysis of oxidized phospholipids in LDL releasing the inflammatory lysophosphatidylcholine (Lyso-PC) and oxidized free fatty acids (Mallat, Lambeau, & Tedgui, 2010). Higher levels of Lp-PLA$_2$ indicate higher chances of plaque rupture, which causes most cardiovascular events (Falk, Shah, & Fuster, 1995; Mauriello et al., 2010). A consensus panel recommended that Lp-PLA$_2$ levels >200 ng/mL be considered to increase Framingham risk scores after finding that they doubled the risk of heart attack and stroke (Davidson et al., 2008).

The PLAC® Test measures Lp-PLA$_2$ levels and is suggested for patients who have any risk factors or need a routine lipid panel done. The test received market clearance by the FDA in 2003, and in December of 2014, it was approved as a screening test for all adults, even those with no history of coronary artery disease (CAD). The American Heart Association, the American Stroke Association, the American College of Cardiology Foundation, and the

American Association of Clinical Endocrinologists all include Lp-PLA$_2$ in their guidelines

(Greenland et al., 2010; Jellinger et al., 2012; Meschia et al., 2014).

The impact of more specific testing has the potential for great significance. According to

the World Health Organization (WHO, 2015), CVD is the number one killer in the United States

and globally, and CAD is the most common and deadly type. Here in America, someone has a

myocardial infarction (MI) every 43 seconds (Mozaffarian et al., 2015). Only screening patients

by checking their lipids is no longer adequate. At least one analysis of hospitalized patients with

CAD revealed that about half of those having a MI had normal cholesterol (Sachdeva et al.,

2009). Conversely, a number of patients (5-20%) with spontaneous MI have minimal or even no

CAD (Thygesen et al., 2012). These last points underline not only the need for greater

specificity, but also the need to recognize modifiable risk factors to aid in prevention through

lifestyle changes.

Cardiovascular risk factors are developing at increasingly earlier ages as the diet and

lifestyle of America's young adults are becoming unhealthier with each generation. The

American Heart Association reveals that modifiable factors such as obesity, hypertension, high

cholesterol, and diabetes are being diagnosed progressively earlier in life (Mozaffarian et al.,

2015). Compounding this, when compared with older adults, young people are less aware of

their health status, less aware that it impacts their future health, and less likely to attribute any

early warning signs to a chronic disease. One study showed that while age-adjusted mortality

from CAD declined steadily from 1980 to 2002, the declines in age-*specific* mortality started

leveling off for young adults, and actually increased from 1997 to 2002 for women in the 35-44

age group (Ford & Capewell, 2007). More recently, Gupta et al. (2014) found that deaths from

acute MI decreased for young women from 2001 to 2010, but hospitalization rates for MI in this

time period stayed the same for young men and women. This long-standing lack of improvement in occurrence highlights that the younger population is insufficiently targeted in primary care and prevention.

There is a limited amount of research on CAD in young adults. The literature review will introduce the pivotal findings on the relationship between CAD and Lp-PLA$_2$, and explore the lifestyle connection that is relatable to the younger population. Possible treatment options through lifestyle changes, and also medicines, are reviewed as well for those with elevated enzyme levels. Following the literature review, this current analysis will look at Lp-PLA$_2$ in a specific study done on a college-aged population with the purpose of examining the significance of the available cross-sectional data on PLAC scores in young adults. Research assistant activities are also described.

Literature Review

Establishment of Clinical Significance

Checking Lp-PLA$_2$ levels in patients may be a newer idea, but the relationship between this enzyme and indicators of cardiovascular disease has been recognized and studied since the 1980s (Farr, Cox, Wardlow, & Jorgensen, 1980; Ostermann et al., 1988; Steinbrecher & Pritchard, 1989). In 2000, *The New England Journal of Medicine* published an analysis from the West of Scotland Coronary Prevention Study (WOSCOPS) that showed for the first time that Lp-PLA$_2$ not only had a strong association with CAD, but also was statistically independent of other inflammatory markers and CAD risk factors (Packard et al., 2000). By 2010, The Lp-PLA$_2$ Studies Collaboration published a meta-analysis in *The Lancet* of 32 prospective studies, which contained over 95% of the pertinent information on Lp-PLA$_2$. They concluded that Lp-PLA$_2$ positively correlated with other inflammatory markers, was associated with CVD in the same

way as non-HDL and systolic blood pressure, and could give distinct insight due to being independent of other markers and risk factors (Thompson et al., 2010). Since this time, the research on Lp-PLA$_2$ has grown exponentially and clinical utilization is starting to increase.

Non-Pharmaceutical Means of Improvement

Many lifestyle choices are made early in life and continue through adulthood. Berenson et al. (1998) showed through autopsies that even children and young adults had atherosclerosis that worsened as the number of cardiovascular risk factors increased. The risk factors of high cholesterol, high blood pressure, poor nutrition, inactivity, obesity, diabetes, excessive alcohol, stress, and smoking are all modifiable through lifestyle changes. Therapeutic changes have been shown to prevent and reverse the effects of CAD. Research is now emerging to support that improving these factors also improves Lp-PLA$_2$ levels. The following are some examples of diet and lifestyle changes affecting this inflammatory marker.

Obesity. Tzotzas el al. (2007) studied obese women without CVD and showed that a low-calorie diet not only lowered weight but also lowered Lp-PLA$_2$. The intervention included young adults with ages ranging from 18 to 63. After four months, a 10.3% reduction in the women's weight resulted in a 10.2% reduction in Lp-PLA$_2$ activity ($p < .01$). Interestingly, the only correlation was with VLDL mass ($r = .39$, $p < .05$) through the weight loss and not LDL or sdLDL, which are typically more associated with Lp-PLA$_2$ (Tzotzas et al., 2007).

Diet and exercise. The confounder of weight was kept in check when a group of HIV patients receiving highly active antiretroviral therapy (HAART) were considered for a study on the impacts of lifestyle modification on Lp-PLA$_2$ due to their increased inflammatory state (Wooten et al., 2013). Young adults, with a minimum age of 21, were included. The participants were randomized into five groups: 1) usual care with two placebos, 2) intensive diet and exercise

(D/E) with two placebos, 3) D/E with active fenofibrate and niacin placebo, 4) D/E with active

niacin and fenofibrate placebo, and 5) D/E with active fenofibrate and active niacin. Weight and

BMI remained constant through the adjustments of dieticians. After 24 weeks, when compared to

the usual care group, Lp-PLA$_2$ was significantly lower in groups 2 ($p < .05$), 3 ($p < .05$), and 4 (p

$< .01$). Although group 5 did not receive this improvement for Lp-PLA$_2$, they were the only

group to have significant reductions in triglycerides ($p < .01$), non-HDL ($p < .05$), and TC:HDL

ratio ($p < .01$), along with an increase in HDL ($p < .01$) when compared to the usual care group

(Wooten et al., 2013). These results argue that Lp-PLA$_2$ may be lowered through diet and

exercise alone, regardless of weight loss or a change in BMI.

Not all have been successful in altering the level through dietary means, however. One

example is a group that found no effect when giving various amounts of fish and olive oils to

their subjects (Pedersen, Koenig, Christensen, & Schmidt, 2009). Further research is needed on

specific diets to find the desired effects on Lp-PLA$_2$.

Nutrition. In a cardiovascular sub-cohort of the ongoing Malmö Diet and Cancer study in

Sweden, Hlebowicz et al. (2011) examined associations between food patterns, inflammatory

markers, and CVD. They narrowed the energy from food consumption, representative of their

large sample size, down to six clusters labeled "'many foods and drinks (MFD),' 'fibre bread,'

'low fat and high fibre (LFHF),' 'white bread,' 'milk fat' and 'sweets and cakes'" (Hlebowicz et

al., 2011, p. 367). In studying Lp-PLA$_2$, they looked at mass and activity. For Lp-PLA$_2$ mass (ng

mL^{-1}), the highest level was in the 'milk fat' cluster for women ($M = 269.25$, $SE = 4.23$) and men

($M = 308.03$, $SE = 4.84$), and the lowest was in the 'LFHF' cluster for women ($M = 250.64$, $SE =$

3.26) and men ($M = 284.55$, $SE = 6.97$). For women, Lp-PLA$_2$ mass was also elevated with high

sugar consumption, and at a 13-year follow-up, there was increased CVD in the 'milk fat' (HR

2.20, 95% CI [1.09, 4.44]) and 'sweets and cakes' (HR 2.14, 95% CI [1.17, 3.93]) clusters. Other

significant findings were that for men, Lp-PLA$_2$ activity (ng mL^{-1}) was best in 'LFHF' (M =

47.58, SE = 1.13), and for women, it was worst in 'white bread' (M = 44.06, SE = 0.70). They

conclude that the best diet for inflammatory markers, and possibly CVD risk, is high in fiber and

low in fat and sugar (Hlebowicz et al., 2011).

   Smoking, drinking, cholesterol, and diet again. Hatoum, Nelson, Cook, Hu, and Rimm

(2010) researched women from the Nurses' Health Study (NHS) and men from the Health

Professionals Follow-Up Study (HPFS), looking at a variety of factors in those without CAD or

cancer. They analyzed the cross-sectional data of laboratory values and lifestyle measurements,

and the combined results found that having a BMI between 25-29.9 kg/m^2 (p < .001), having

high cholesterol (p < .001), taking aspirin (p < .01), and smoking (p < .001) were all significantly

associated with elevated levels of Lp-PLA$_2$. Drinking a moderate amount of alcohol lowered Lp-

PLA$_2$ (p < .001). In women, postmenopausal hormone use was also associated with a lower level

(p < .001). The study found that cholesterol-lowering medication only lowered Lp-PLA$_2$ in those

with a history of high cholesterol (p < .05), and it actually appeared to raise the level in the small

number that took medication without a history of high cholesterol. Another interesting dietary

finding was that replacing carbohydrate consumption with protein was associated with decreased

Lp-PLA$_2$ activity (p < .05), and more importantly, that protein appeared to have an effect on Lp-

PLA$_2$ unrelated to the expected changes in lipid concentrations (Hatoum et al., 2010).

Pharmaceutical Means of Improvement

   While lifestyle changes are effective for many, those at increased risk may need help

through medications. Statins have been shown to lower Lp-PLA$_2$ levels, at least in those with

elevated cholesterol (Hatoum et al., 2010). Results from an analysis of the Long-Term

Intervention with Pravastatin in Ischaemic Disease (LIPID) study revealed that pravastatin reduced the level by 16% after one year while the placebo reduced it by 0.4% ($p < .001$). More importantly, this was found to have an equal or greater impact than LDL reduction on CHD death and heart attacks (White et al., 2013). Ryu et al. (2012) did a substudy of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial and found that atorvastatin lowered median Lp-PLA$_2$ mass (-35.8%) and activity (-24.3%) more than a placebo (-6.2%, 5.4% respectively; $p < .001$) after just 16 weeks on an 80 mg dose. Rosuvastatin has also displayed good results, along with ezetimibe and fenofibrate (Agouridis et al., 2011; Saougos et al., 2007). The Lp-PLA$_2$ inhibitor darapladib failed the STABILITY and SOLID-TIMI 52 trials over the past couple of years leaving out the option for now of a specific Lp-PLA$_2$-lowering drug (O'Donoghue et al., 2014; White et al., 2014).

Summary

Lp-PLA$_2$ has been established as a critical inflammatory biomarker. Basic lipid panels are becoming insufficient to test for CVD. Half of those having a MI have normal cholesterol (Sachdeva et al., 2009). While there is more research on pharmaceutical methods of treatment for elevated levels of Lp-PLA$_2$, the available diet and lifestyle studies show that there is at least some degree of relationship in these areas. For young adults, this is a good place to begin when discussing prevention and early treatment options. It has been shown that Lp-PLA$_2$ activity has a positive association with age (Hatoum et al., 2010). Even for those that will not experience a cardiovascular event when they are young, their current lifestyle choices are known prognosticators for having one later in life. The chronic and progressive inflammatory characteristics of disease point to a correlation with lifestyle factors and the need for earlier primary prevention.

Methodology

In 2014, research was conducted on student volunteers of the Zoe Transformation, a 28-day wellness challenge that took place at Southern Adventist University (SAU). The purpose of the study was to examine the effects of a whole-food plant-based diet on cardiovascular markers and spirituality. Among the laboratory values, levels of Lp-PLA$_2$ were examined by measuring PLAC scores before and after the 28-day period. The researchers also used various questionnaires, scales, and interviews. They hypothesized that the tests and measurements would improve over the study period, and the spiritual component would enhance the participants' resolve during the challenge.

Theoretical Framework

The SAU School of Nursing utilizes the Neuman Systems Model (NSM) for its emphasis on a comprehensive view of health. The NSM is also appropriate as a theoretical framework for the Zoe Transformation with its focus on prevention and health promotion. The individual participants' stressors and environments were factored into the study, consistent with the model. Neuman's physiological, psychological, sociocultural, developmental, and spiritual variables were all addressed in the challenge (Neuman, 2005). The Zoe study evaluates the effects of lifestyle elements (diet, stress, physical activity, spirituality, etc.) on the health of college students.

Design

For this exploratory quasi-experimental study, a pre-test/post-test was used to evaluate the effects of a faith-based, 28-day lifestyle transformation program on cardiovascular markers and spirituality.

Sample

Any SAU student that was registered at the time of the study was permitted to participate. Volunteers were recruited by email and also by a verbal presentation at the program launch. There were a total of 79 student participants. The experimental group contained 52 subjects, and the control group contained 27. Of the total, 19 individuals (10 experimental, 9 control) had their Lp-PLA$_2$ checked with the PLAC Test at the beginning of the study (Pre-PLAC), and 13 (8 experimental, 5 control) checked it at the end (Post-PLAC). All that had a Post-PLAC drawn were from the 19 that had a Pre-PLAC done, except for one subject in the experimental group.

Tools

The researchers used various tests, self-reporting scales and questionnaires, and interviews to collect information at the beginning and end of the study. The resting metabolic rate was tested by the Parvo Medics TrueOne 2400 Metabolic Measurement System in the SAU Human Performance Lab under the supervision of Dr. Harold Mayer. Blood tests used were plasma cortisol levels, C-reactive protein, lipids, and PLAC. These samples were collected by the researchers and taken to University Health Services for processing by PathLab. The Dietary Screener Questionnaire (DSQ), containing 30 questions, gathered information on each participant's food group selection and frequency for the previous month. The Short Last 7 Days Self-Administered version of the International Physical Activity Questionnaire (IPAQ) was used to evaluate activity level in seven questions covering the vigorous, moderate, light, and sedentary categories. The 14-question Perceived Stress Scale (PSS) measured the response to specific stressors over the past month. The Daily Spiritual Experience Scale (DSES) was the first tool used for the spiritual component of the study with its 15 items assessing the influence of God in everyday life. The interviews were the other method by which the spiritual experience was

explored. These were only done at the end of the 28-day period and contained four open-ended questions.

Ethics

The SAU Institutional Review Board approved the research project. Efforts were made to keep personal information confidential, and no personal identifiers were collected. Identifiers were translated to a code, and letter identifiers were used for the interviews. The potential physical and psychological risks from the tests were considered minimal. Participation was voluntary and students were able to choose which components to engage in. Informed consent was obtained from all participants.

Analysis

All analyses were performed using SPSS version 22. A p value less than .05 was considered to be statistically significant.

Results and Discussion

Research Assistant

As a research assistant, my initial involvement was compiling and increasing the available research on Lp-PLA$_2$ for the School of Nursing at Southern Adventist University. An emphasis was placed on articles that showed a relationship between Lp-PLA$_2$ and lifestyle, as this area was found most lacking. Research was also sought out that was directed towards, or included, young adults. The other main area of work as research assistant included assumption and correlation testing on ZOE cross-sectional PLAC data using SPSS.

Findings

The ZOE study is nearing completion, but the data analysis was still ongoing at the time this paper was submitted.

Evaluation

There was a clear benefit from working in a focused area of study over an extended period of time. A greater understanding of Lp-PLA$_2$ was obtained in this process, and also a small glimpse of the complex, pervasive condition of chronic inflammation. The ZOE study has been unique with its utilization of graduate students, which has changed the hands of those working on different components as each semester progresses. The efforts and sacrifices of individuals working on a research team have been increasingly recognized and valued by the successive participants.

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