Communication

A Novel Clinical Entity: Triglyceride Deposit Cardiomyovasculopathy — Implications and Perspectives from “Obesity of the Heart”

Ken-ichi Hirano

Department of Cardiovascular Medicine, Graduate School of Medicine, Osaka University, Osaka, Japan

Heart diseases, including atherosclerotic cardiovascular disease and congestive heart failure, are major life-threatening disorders in most countries. Cholesterol is a vital causal factor and focus of research into heart diseases, but the involvement of triglycerides remains unclear. We recently reported a unique patient suffering from severe congestive heart failure and needing cardiac transplantation. Massive accumulation of triglycerides was observed in coronary atherosclerotic lesions as well as in the myocardium, while plasma triglyceride levels were normal. We suggested that this phenotype was a novel clinical entity and named it “Triglyceride deposit cardiomyovasculopathy”, or simply “Obesity of the heart”. The patient was identified as homozygous for a genetic mutation in the adipose triglyceride lipase, an essential molecule for hydrolysis of intracellular triglycerides. The present paper deals with what we can learn from this single case and discusses its implications for research and clinical medicine related to heart diseases.


Key words; Adipose triglyceride lipase, Atherosclerosis, Cardiac transplantation, Congestive heart failure, Triglycerides, Triglyceride deposit cardiomyovasculopathy

Cholesterol has been a principal focus of heart disease research during the last 50 years. The Framingham heart study, which started in 1960, reported that plasma cholesterol levels were a strong predictor for coronary heart disease. In the 1970s, Brown and Goldstein clarified the molecular mechanism for familial hypercholesterolemia (FH) and indentified the low density lipoprotein (LDL) receptor as the molecule responsible for FH. In the same decade, Endo et al. discovered fungal metabolites with hypocholesterolemic activities, which were the prototype of what are currently called “statins”. Recently, clinical studies with “power statins” showed that almost half of all cardiac vascular events and deaths can be prevented with these kinds of drugs. Recent reports seem to indicate that statins may be effective for non-ischemic as well as ischemic congestive heart failure.

In contrast to cholesterol, the involvement of tri-

Address for correspondence: Ken-ichi Hirano, Department of Cardiovascular Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
E-mail: khirano@imed2.med.osaka-u.ac.jp
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Glycerides (TG) in heart diseases has remained ambiguous. In spite of their best efforts, it has been difficult for researchers to obtain direct proof of an association between plasma TG levels and coronary heart disease. Before the Framingham heart study and the aforementioned two major discoveries of LDL receptors and statins, pathologists had reported that the human aorta and coronary arteries contained substantial amounts of TG, comparable to cholesterol; however, it seems that the big cholesterol “wave” swept TG away from the heart to the adipose tissue.

TG is synthesized from glycerol and fatty acids and hydrolyzed by intracellular lipases (i.e., adipose triglyceride lipases (ATGL)) and extracellular lipases (i.e., lipoprotein lipases). Adipocytes take up long-chain fatty acid (LCFA), synthesize TG, and store them in cytoplasmic lipid droplets as a major energy source for the whole body. When required, TG is hydrolyzed by lipases and LCFA is delivered through the bloodstream to oxidative tissues, such as the heart and some skeletal muscles. The heart, which must beat approximately one hundred thousand times a day, prefers LCFA to produce adenosine triphosphate (ATP) via mitochondrial β-oxidation in order to achieve maxi-
triglyceride deposit cardiomyovasculopathy (TGCV) or simply “Obesity of the Heart” (Fig. 1A). It is interesting that the phenotype of TGCV is very similar to that of ATGL knockout mice generated by Zechner et al.\textsuperscript{13}.

What can we learn from this single case of “Obesity of the Heart”?  
1. We need to be aware of the presence of a substantial amount of TG in human arteries. 
2. It is difficult to differentiate TG from cholesteryl ester by using conventional Oil red O or Sudan IV staining methods. For example, Oil red O-positive lipids in arteries may not always be cholesteryl esters, but rather TG.
3. As mentioned earlier, it seems difficult to prove a direct association between plasma TG levels and coronary heart disease. We need to consider that tissue TG content may depend on intracellular catabolism (hydrolysis) of TG mediated by lipases (ATGL etc) rather than on a supply from substrates such as LCFA from plasma (Fig. 1B).
4. The frequency of TGCV phenotype occurrence may be higher in Japan. Since the 1980s, cases of Jordan’s anomaly have been reported in Japan in which patients suffered from cardiomyopathy associated with neutral lipid deposition, although their
molecular basis was not identified\textsuperscript{14-16}. More recently, it was reported that patients with ATGL mutation had severe heart disease\textsuperscript{17, 18}, but without mention of TG deposition in coronary arteries.

Possible implications for research and clinical medicine:
1. Elucidation of pathophysiology of TGCV
2. Investigation of the initiation and progression of atherosclerosis in TGCV, particularly focusing on the difference between atherosclerosis in TGCV and classical atherosclerosis, described by Ross et al.\textsuperscript{19, 20}
3. Determination of the relevance of TGCV phenotype. For this purpose, a population with a high prevalence of TGCV needs to be found.
4. Identification of primary and secondary causes of TGCV
5. Development or laboratory test or other method for easy evaluation of tissue TG accumulation.
6. Examination of the relationship between TG deposition in the heart and acute coronary syndrome.

Medical science has seen novel hypotheses put forward and breakthroughs achieved, such as those for FH\textsuperscript{21} and Tangier disease\textsuperscript{22}, as a result of patient-oriented research\textsuperscript{23}. “Cholesterol and atherosclerosis” seem to be close to the goal, whereas “Inflammation and atherosclerosis” are the subject of heated discussion\textsuperscript{24}. This single reported case may indicate that this is a suitable time to ask whether “TG” comes back from adipose tissue to the heart.

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