Continuous effort—not strength or intelligence—is the key to unlocking our potential—Winston Churchill—we are still underway to find biomarkers in cardiovascular diseases

It is not necessary to stress how the biomarker is necessary in various fields of medicine and research fields. Recent coronavirus disease (COVID) pandemic reassured the importance of biomarkers in public health and epidemiological studies. Classical inflammatory markers or organ specific markers such as C-reactive protein (CRP), Ferritin, interleukin-6 (IL-6), Troponin, Neutrophil/lymphocyte ratio and so on are focused. In the field of non-communicable diseases (NCDs), inflammation plays a pivotal role in disease progression. At the same time, progresses in large clinical trials and genetical analysis both in gene mutation and epigenetical regulations, the importance of personalized medicine emerged. In the field of personalized medicine, biomarkers also play a key role. By analyzing an individual's unique biomarker profile, healthcare providers can tailor treatments and increase the efficacy as well as reduce adverse effects.

The biomarkers are required to fulfil several needs such as (I) high sensitivity and specificity, (II) accuracy and precision, (III) non-invasiveness and cost effective, (IV) stability and robustness of samples, (V) validation and reproducibility and for clinical application, (VI) feasibility and availability with wide dynamic range. To establish new biomarkers tremendous and rigorous works are required and good collaborations between academia and industries.

In this series of reviews in biomarkers in cardiovascular disease, four experts and their group performed a review of both clinically applicable recent biomarkers and advances in upcoming possible biomarkers.

Mujadzic *et al.* reviewed biomarkers for hypertension, a most common risk for cardiovascular diseases (1). Measuring blood pressure (BP) has become possible in the early 20th century by the method established by Korotokoff and Riva-Rochi and that method had been used for more than a hundred years, however, recent advances and the Minamata treaty, sphygmomanometer has disappeared from our clinic and electrically measurement using oscillometric method is widely used these days (2). This method enabled the patients to monitor their BP at home, the ultimate point of care testing (POCT), and studies revealed the importance of home BP, night time BP or morning BP in cardiovascular events (3). Human heartbeat per day is about 0.1 million and we have 0.1 million of BP in a day and accumulation of high BP burden is a risk for cardiovascular events. Using home BP monitoring, we can collect more data of BP and can evaluate the burden, however, it is not enough. In the case of diabetes, we use HbA1c or glycated albumin for evaluating 1 to 2 months average blood glucose level. In contrast in hypertension, we do not have such proper biomarkers. Left ventricular hypertrophy, proteinuria, vascular function tests [flow-mediated dilatation (FMD) test, cardio ankle vascular index (CAVI), pulsewave velocity (PWV)] or fundal vasculopathy are markers but they reflect long term BP effect and are not suitable for treatment response assessment (3). The literature review by Mujadzic (1) revealed there are some possible circulatory regulating peptides that can predict the future development of hypertension and risk assessment. Also, classical urinary albumin, CRP and brain natriuretic peptide (BNP) can be used but not satisfied to predict prognosis or to assess the short-term treatment responses. Laragh and his colleagues suggested renin level can be used for personalized medicine in hypertensives (4), however, the validation study failed to show its usefulness (5). The door is widely opened for researchers to find new biomarkers for hypertensives, which one-third of the population suffered all over the world and its prevention as well as good control can save our lives.

Yoshioka *et al.* reviewed albumin as a biomarker for cardiovascular disease, mainly in ischemic heart disease (6). Albumin is used for monitor several disease conditions and its specificity for NCDs is rather low, and we must pay high attention for confounding factors when we evaluate studies on albumin and diseases. In this review, low albumin level is shown to be a risk for ischemic events but it is controversial whether albumin is increased prognosis improves. As mentioned above, albumin lysine residues are glycated and measured as glycoalbumin to monitor diabetes control and its cysteine residues are oxidated and there are two types of albumin, namely oxidized and reduced albumin. Yasukawa and her colleagues revealed that the quality of albumin is more important than the quantity of albumin; poor quality with high oxidized albumin is a risk for multiple NCDs (7-10). So far, we do not have tools to reverse oxidized albumin to reduce one, future studies are required to establish oxidized albumin can be a better marker for cardiovascular as well as other NCDs.

Kamijo-Ikemori *et al.* reviewed tubular markers in kidney diseases (11). The concept of chronic kidney disease (CKD) is now widely accepted and in CKD, urinary protein and glomerular filtration rate is focused. However, the tubular function of the kidney controls physiologically more important factors such as volume, electrolytes, acid-base balance, uric acid and others that are closely related to cardiovascular diseases. In her review, she picked up tissue inhibitors of metalloproteinases-2 (TIMP-2), insulin-like growth factor binding protein-7 (IGFBP7) and L-type fatty acid binding protein (L-FABP) which she originally reported its importance in renal dysfunction. TIMP-2 and IGFBP7 is widely used for diagnosis of acute kidney injury (AKI) which was believed to be reversible and do not progress to CKD, however, a recent study showed AKI is a risk for CKD and cardiovascular events (12). In contrast, L-FABP reflects oxidative stresses in the tubules and a marker for not only AKI but for CKD. All three markers are measured in urine, which is non-invasive than blood test and POCT kit is developed for L-FABP for earlier detection of deterioration of tubular function. These markers meet the prerequisites of biomarker which are feasibility and safety. The usefulness of epigenetical markers in urinary sediment is reported (13). DNA methylation patterns to identify tubular cell damages are used for this study and it can be a marker for deterioration of diabetic kidney disease, a leading cause of hemodialysis. The further studies are required if the treatment of diabetic kidney disease by mineralocorticoid antagonists or other agents alters epigenetical markers or alteration of those markers can be utilized for precision medicine.

Finally, Kimura *et al.* reviewed lipid-related novel markers for cardiovascular diseases (14). Statins can lower low-density lipoprotein (LDL) cholesterol and prevent cardiovascular events, however, there still remain high-risk patients under statin therapy. Triglyceride can be another risk to lower, however, several clinical trials failed to show positive results in triglyceride targeting therapy. And now it is focused on lipoprotein lipase (LPL) regulation. In this review, the relationships between triglyceride metabolism-related proteins and atherosclerosis such as LPL, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), chylomicron, and very-low-density lipoprotein (VLDL). LPL is downregulated in high-risk patients and preheparin LPL can be a good marker for efficacy of triglyceride lowering therapy. Heparin releases LPL from endothelial cells and LPL from heparin-treated patients are unstable and does not meet the requirement for biomarker, stability of sample. Heparin-nontreated sample may be a better biomarker in patients with high in triglyceride.

Looking for biomarkers in NCDs is still underway and more researchers and collaborations with industry to develop measurement method is required.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Laboratory and Precision Medicine* for the series "New Biomarkers in Non-communicable Diseases". The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-23-44/coif). The series "New Biomarkers in Non-communicable Diseases" was commissioned by the editorial office without any funding or sponsorship. TS served as the unpaid Guest Editor of the series and serves as an unpaid Associate Editor-in-Chief of the *Journal of Laboratory and Precision Medicine* from September 2023 to August 2025. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

References

1. Mujadzic H, Skeete J, DiPette DJ. Historical, present, and emerging biomarkers in hypertension: a narrative review. J Lab Precis Med 2022;7:32.
2. Shimosawa T. Quality is not an act, it is a habit-Aristotle. Hypertens Res 2023;46:1221-6.
3. Mancia Chairperson G, Kreutz Co-Chair R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH). J Hypertens 2023;41:1874-2071.
4. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Am J Hypertens 2001;14:186-94.
5. Weintraub HS, Duprez DA, Cushman WC, et al. Antihypertensive response to thiazide diuretic or angiotensin receptor blocker in elderly hypertensives is not influenced by pretreatment plasma renin activity. Cardiovasc Drugs Ther 2012;26:145-55.
6. Yoshioka G, Tanaka A, Goriki Y, et al. The role of albumin level in cardiovascular disease: a review of recent research advances. J Lab Precis Med 2023;8:7.
7. Yasukawa K, Shimosawa T, Okubo S, et al. A simple, rapid and validated high-performance liquid chromatography method suitable for clinical measurements of human mercaptalbumin and non-mercaptalbumin. Ann Clin Biochem 2018;55:121-7.
8. Chou S, Yasukawa K, Fujino Y, et al. Non-mercaptalbumin is significantly associated with the coronary plaque burden and the severity of coronary artery disease. Sci Rep 2021;11:14242.
9. Fukuhara S, Yasukawa K, Sato M, et al. Clinical usefulness of human serum nonmercaptalbumin to mercaptalbumin ratio as a biomarker for diabetic complications and disability in activities of daily living in elderly patients with diabetes. Metabolism 2020;103:153995.
10. Nakatani S, Yasukawa K, Ishimura E, et al. Non-mercaptalbumin, Oxidized Form of Serum Albumin, Significantly Associated with Renal Function and Anemia in Chronic Kidney Disease Patients. Sci Rep 2018;8:16796.
11. Kamijo-Ikemori A, Kimura K. Clinical utility of tubular markers in kidney disease: a narrative review. J Lab Precis Med 2022;7:27.
12. Muiru AN, Hsu JY, Zhang X, et al. Risk for Chronic Kidney Disease Progression After Acute Kidney Injury: Findings From the Chronic Renal Insufficiency Cohort Study. Ann Intern Med 2023;176:961-8.
13. Marumo T, Hoshino J, Kawarazaki W, et al. Methylation pattern of urinary DNA as a marker of kidney function decline in diabetes. BMJ Open Diabetes Res Care 2020;8:e001501.
14. Kimura T, Tsunekawa K, Nagasawa T, et al. Circulating levels of lipoprotein lipase and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1: new markers for cardiovascular diseases among noncommunicable diseases: a brief narrative review. J Lab Precis Med 2023;8:18.

Tatsuo Shimosawa

Tatsuo Shimosawa[1,2], MD, PhD

[1]Department of Clinical Laboratory, Faculty of Medicine, International University of Health and Welfare, Narita, Chiba, Japan; [2]Department of Clinical Laboratory, Narita Hospital, International University of Health and Welfare, Narita, Chiba, Japan.

(*Email: tshimo-tky@umin.ac.jp*)

Keywords: Hypertension; ischemic heart disease; chronic kidney disease (CKD); atherosclerosis

Received: 17 July 2023; Accepted: 16 August 2023; Published online: 30 August 2023.
doi: 10.21037/jlpm-23-44
View this article at: http://dx.doi.org/10.21037/jlpm-23-44

doi: 10.21037/jlpm-23-44
Cite this article as: Shimosawa T. Continuous effort—not strength or intelligence—is the key to unlocking our potential—Winston Churchill—we are still underway to find biomarkers in cardiovascular diseases. J Lab Precis Med 2023;8:25.