



**Orange Biomed Co-Founder Dr. Unghyeon Ko (left), CEO Yeaseul Park (right)**

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# GLYCATED HEMOGLOBIN BIOMARKER PREVENTS DIABETIC COMPLICATIONS

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Reporter: Park Soo-Yeon

Orange Biomed developed a glycated hemoglobin analyzer using microfluidic technology the size of red blood cells. We met CEOs Yeaseul Park and Dr. Unghyeon Ko and discussed the current status of people with diabetes and the innovation of microfluidic technology.

Diabetes without early symptoms is easily overlooked, but the seriousness of the disease is by no means easy. For people with diabetes, the production and activity of insulin (a hormone that helps control blood sugar levels) keeping the amount of glucose in the blood constant decreases, so diabetes complications can occur if not managed in time.

When a large amount of sugar is bound to the hemoglobin in the red blood cells of a person with diabetes, the level of glycated hemoglobin increases, which in turn increases the stiffness of the red blood cells and the viscosity of the blood. Patients should continue treatment with diet and exercise, and check blood sugar and glycated hemoglobin levels just like measuring body temperature and weight for health management. In particular, many studies have shown that glycated hemoglobin is closely related to diabetes complications. We recently met and talked with the two co-founders of Orange Biomed, which developed a glycated hemoglobin monitor that can be used at home.

**Q. Along with blood sugar, glycated hemoglobin is known as a value that people with diabetes must know. (Normal 5.6% or lower, Diabetes 6.5% or higher) Is there a reason why Orange Biomed chose HbA1c research as its first start?**

**Park:** We first paid close attention to people with diabetes. In the United States alone, 11% of the population has diabetes and 33% have pre-diabetes, so overall more than 40% are at risk of diabetes or are in the high-risk group. In Korea, as of 2020, there are 6 million people with diabetes and more than 15 million high-risk groups. When we meet people to verify ideas, most of them or their family members are living with diabetes. Because diabetes has few early symptoms, it is often not recognized by a doctor until it becomes severe. CEO Dr. Ko and I met at Duke University, so we had many opportunities to meet people with diabetes in the southern United States.

I was surprised to learn that there are so many people with severe symptoms. They tend to live with anxiety about the potential complications that could occur. Glycated hemoglobin is a great measure to prevent diabetes complications. In fact, even if the level of glycated hemoglobin is brought down by only 1%, it is said that the incidence of various complications can be greatly decreased, such as reducing the mortality rate by 21%, and the incidence rates of cardiovascular disease by 14%, peripheral vascular disease by 37%, and retinopathy by 19%.

**Ko:** As CEO Park said, the correlation between glycated hemoglobin levels and diabetes complications has been scientifically proven through the Diabetes Control and Complications Trial (DCCT). Interestingly, this strong association was not found with blood glucose levels, which are often measured in patients. In addition, the measurement of glycated hemoglobin is well standardized through the National Glycohemoglobin Standardization Program (NGSP); diabetes can be diagnosed if the level is above a certain level. For this reason, the diabetes academic communities also recognize glycated hemoglobin as an important biomarker, and the American Diabetes Association (ADA) website emphasizes the importance of glycated hemoglobin in diabetes management.

**Q. It is known that the existing glycated hemoglobin measurement methods mainly use immunoassay and chromatography in hospitals. What is the difference between 'OBM rapid A1c', Orange Biomed's glycated hemoglobin analyzer, and the existing methods?**



### **Orange Biomed's glycated hemoglobin meter 'OBM rapid A1c'**

**Park:** A prototype was released in January of last year. Unlike the existing methods, the device we developed has the advantage of being portable and easy to use by anyone. 'OBM rapid A1c' can achieve a similar level of accuracy at 1/500th the price of HPLC equipment used in large hospitals. Above all, it does not affect accuracy even if it is used by caregivers or patients other than medical staff in a non-hospital setting.

HPLC (high-performance liquid chromatography) is equipment that costs \$75,000+ and is typically only used in large hospitals. It has the principle of separating hemoglobin in the blood by type (refining protein) and measuring the proportion of normal hemoglobin to glycated hemoglobin. Because it determines exactly how much protein is in it, operating the equipment is technically difficult. To replace this device, some local hospitals use a bench-top device (a smaller device that can be placed on a table) that costs \$3,000+. Although it offers benefits such as obtaining test results immediately at the point of care, this type of device sacrifices accuracy compared to HPLC devices. In the immunoassay method, devices use antigen-antibody reactions, which also require high maintenance work. After all, The aforementioned devices or methods are difficult to maintain, making it inaccurate when used by non-professionals or at home.

**Q. It is important to reduce the error of the glycated hemoglobin meter. You said that microfluidic technology maintains accuracy without being affected by the environment because it does not use antibodies or protein reagents. How was the microfluidic technology in the 'OBM rapid A1c' made?**

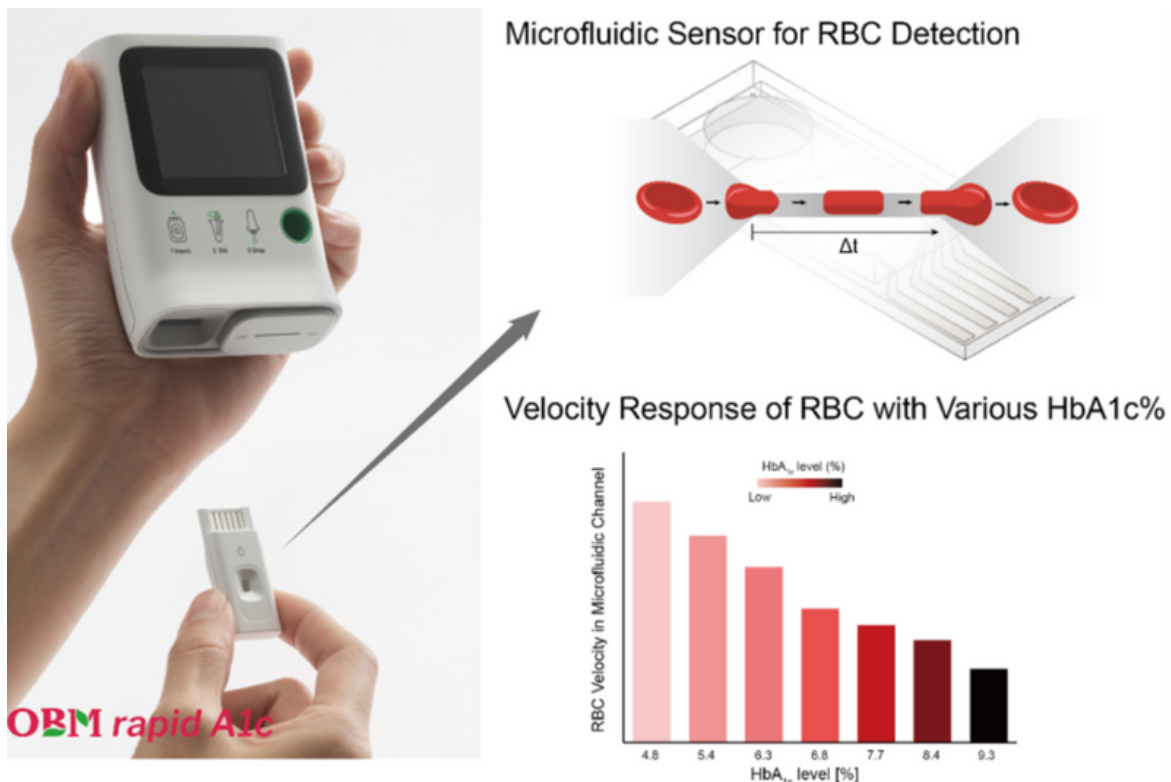
**Ko:** My main field of research is cell mechanics or mechanobiology. In this field, research is conducted to measure how hard and how viscous a cell is by stretching and pulling the cell. So I thought about what it would be like to measure glycated hemoglobin using the stiffness of red blood cells from a different perspective. However, red blood cells are very small and physically unwieldy. The existing technique of measuring the stiffness of each red blood cell was very labor intensive and had a problem with a large margin of error. For that reason, it was difficult to obtain statistically significant results by measuring the stiffness of a large number of red blood cells at once. Therefore, we have developed a system that can control a large amount of cells at once through microfluidic technology and measure and compare stiffness. Our system measures the stiffness of red blood cells using a microfluidic system that is smaller than red blood cells and calculates the level of glycated hemoglobin. It is the first and only technology in the world that directly calculates the HbA1c level using the stiffness of red blood cells.

**Park:** Hemoglobin is originally in a soft state, but when glycated, red blood cells containing hemoglobin become hard. In a soft state, it passes through blood vessels easily. However, when it becomes hard it cannot pass through blood vessels properly, blocking or damaging the capillaries. That can cause diabetes complications. Existing instruments measure the concentration of hemoglobin, not the stiffness, so it was largely affected by the volume. The concentration varies depending on how much blood sample is drawn. For example, most of them require 1 to 3 microliters (microliter,  $\mu\text{L}$ : 1 millionth of a liter), and if you accidentally draw 5 microliters, a significant error may occur.

It has to be measured in the exact sample volume. Also, when measuring glycated hemoglobin, only those targeted by the antibody should be filtered out, but there is an interference effect in which similar proteins mistakenly attach. As one filters out all the similar-looking proteins, one can't get the exact concentration of the target protein. As devices get smaller and smaller, the accuracy decreases due to interference effects. Since our 'OBM rapid Alc' does not use any protein, it is not affected by the concentration or amount of blood collected and is free from interference effects.

**Q. Overseas, other manufacturers have launched a professional-use POC device with a smartphone app function. Various functions are added to provide additional information related to glycated hemoglobin. I heard that Orange Biomed focused on core functions and removed all other functions. Is there an intention to focus only on the core?**

**Park:** Yes, we have considered those functions as well in the planning phase. During our planning period, we were able to add several functions. However, this inevitably complicates usability. Our focus was to create a guided device that makes it as simple as possible for older age groups to measure glycated hemoglobin, easily at home. Beyond the power button, there are no other buttons, making it simple for any user. When you turn on the power, a slot for inserting a cartridge appears, and the user inserts the cartridge, dilutes the collected blood, and drops it in. This method is borrowed from the COVID-19 kit method. People were exposed to a lot of self-diagnosis kits during the pandemic. After noting the familiarity and ease of use of these kits, we had the idea to create a similar design.



### The Microfluidic System of 'OBM rapid A1c'

Of course, we also made it similar to the existing blood glucose meters on the market. Blood glucose meters are also measured by inserting a strip into the device and applying the blood to it.

**Q. Orange Biomed's glycated hemoglobin measurement device seems to be a good product for individual use. However, I think it will be useful in small hospitals that cannot afford expensive equipment or public health centers in countries where medical environments are lacking. Who is the target for Orange Biomed's products?**

**Park:** We consider patients, small and medium-sized medical institutions, and public health centers as our targets. A family history of diabetes is recognized as an important risk factor for the disease. If someone in your family has been diagnosed with diabetes, it is recommended for you to check your A1c level regularly. If you have this device for home use, the whole family can use it. Our goal is to increase access to help with early detection, early prevention, and treatment before serious complications develop.

According to U.S. statistics, people who live in areas with poor access to hospitals have a higher risk of diabetes complications because they tend to check their A1c level less frequently.. One-fourth of all medical expenses in the United States are related to diabetes, meaning the burden of medical expenses is high. The same is true in Korea. In the U.S. there are some services that provide blood tests through the mail. It shows the patients' needs for at-home blood tests. I tried one of the test kits.

However, the amount of blood that had to be drawn was 300 microliters, which is 100 times more than our A1c meter requires. It was not asking for a single drop, but the level of shedding blood. In the end, I could not complete the test because it was too hard to collect enough sample. Despite this issue, there is still strong demand for these at-home A1c testing services on the market.

**Ko:** And, crucially, there are legal restrictions on the use of postal services across the country. In some areas sending blood by mail is prohibited. This prolongs the issue for people with diabetes who need the services but are not able to get them due to poor access to hospitals.

**Park:** The first reason why we target the U.S. market is because of the medical system. There are 133 million people with diabetes and access to medical care is not enough. In Korea, if you want to, you can go to the hospital and get your A1c level tested for less than \$8. In the US, it can cost \$200 without insurance. The burden of medical costs and accessibility in the U.S. is a serious problem, so I set it as the first target. We are planning to supply not only the United States and Korea, but other countries where medical devices are difficult to be distributed or supplied. As explained earlier, since our device does not use protein, it has more freedom in terms of logistics and longer shelf life. All you need is a battery and the device requires no maintenance. It is easy to bring into countries with hot climates. You can buy and store several disposable cartridges, and you can utilize courier services without the inconvenience of cold chain distribution, as required for items such as vaccines.

**Q. Do you have any future development plans using Orange Biomed's microfluidic technology? I am curious about the future schedule of Orange Biomed.**

**Ko:** We continue to consider what kind of research to conduct in the future with advanced microfluidic technology. Our technology not only measures the stiffness of red blood cells but also distinguishes the types of cells in the blood. Currently, it is expected that it will develop into a CBC test screening device that can easily perform a complete blood count (CBC) with a single drop of blood. In addition, it seems that it can be used as a device to detect circulating tumor cells (CTC) floating in the blood since the stiffness of the cells can be measured. Lastly, since microfluidic technology is a microtubule, it has a very large surface area. It has a surface area similar to that of a capillary. A device that uses such a large surface area to filter impurities in the blood, such as a new type of microfluidic kidney dialysis machine (POC device) that mimics a kidney and enables rapid hemodialysis in a hospital or at home, is also being considered as a future device.

**Park:** Our device is currently undergoing a second clinical trial at Asan Medical Center. We are accumulating data by comparing and analyzing data values obtained from Asan Medical Center's HPLC equipment and those obtained from 'OBM rapid A1c'. Accurate measurement becomes more possible as data accumulates. The hospital provided a lot of assistance, so we were able to speed up development and additional clinical trials. Orange Biomed's mission is to bring happiness to the daily lives of those with diabetes. with technology that benefits individuals across the globe.

Chronic diseases require constant management, which is easier said than done for patients. It interferes with one's daily life because they have to pay attention to each and every food they consume, in addition to other daily concerns. In the case of glycated hemoglobin, which must be measured every three months, it is inevitable to be interrupted in work or school due to required hospital visits. We want to help these patients so that there is no disruption to their daily life. The goal is to conduct clinical research in the United States in the short term and obtain U.S. FDA clearance with verifiable data. In the long term, we want to continue to develop new medical devices to help save more patients' lives.

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