



REVIEW ARTICLE

Importance and Feasibility of Point-of-care Testing in Takayasu's Arteritis

Sakshi Mehta, Veena Dhawan*

Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

*Corresponding Author: Prof. Veena Dhawan, **Email:** officialveenapgi@gmail.com, **Tel:** 91-172-2747585

Received: February 26, 2020; **Accepted:** April 17, 2020; **Published:** April 30, 2020 **DOI:** 10.36922/itps.v3i1.906

Copyright: © 2020 Mehta and Dhawan. This is an open-access article distributed under the terms of the Attribution-NonCommercial 4.0 International 4.0 (CC BY-NC 4.0), which permits all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract: Takayasu's arteritis (TAK) is known to be a unique, rare, and chronic vasculitis disease that affects large elastic arteries such as aorta and its major branches. TAK is characterized by adventitial thickening, weak pulses and ocular disturbances. The prognosis and diagnosis of TAK are challenging due to the non-specific, silent, or paucisymptomatic presentation of the disease. The effective understanding of TAK lies with the timely recognition of the symptoms and a rapid diagnosis of the disease. Point-of-care testing (POCT) is vital for the quick and reliable detection of parameters near bedside for disease diagnosis, assessment, monitoring, and therapeutics management. Ultrasonography is the most reliable POCT technique. Moreover, erythrocyte sedimentation rate and C-reactive protein assay are the two most valuable non-imaging POCT tests used to determine inflammation and onset of the disease. Other potential biomarkers such as matrix metalloproteinases, soluble receptor for advanced glycation end products, interleukin (IL)-6, and IL-18 have also been advocated for tracking the progression of TAK. Furthermore, vasculitis associated-anti-neutrophil cytoplasmic antibodies have also been reported to reflect the inflammatory phase of the disease. Therefore, the development of POCT based on these blood-based biomarkers may help in quick clinical decision-making for early diagnosis of TAK and targeted therapeutics to improve clinical outcome in patients suffering from this debilitating disease.

Keywords: Takayasu's arteritis, Point-of-care testing, Biomarkers, Imaging techniques

This article belongs to the *Special Section: Point-of-Care Testing Tool Development in Health and Disease*.

1 Takayasu arteritis

Takayasu's arteritis (TAK) is recognized as a rare and chronic inflammatory vasculitis that affects large arterial blood vessels and its main branch arteries [1,2]. TAK is basically a form of granulomatous arteritis which is characterized by weak pulses and ocular disturbances [3]. TAK is commonly referred to as a pulseless disease and non-specific aortic arteritis. The Chapel Hill Consensus Conference (1994) defined TAK as "granulomatous inflammation of the aorta and its

major branches" based on the Nomenclature of Systemic Vasculitis [4].

TAK was first reported in a 21-year-old female as "coronary anastomosis," characterized by an arteriovenous anastomosis around the papilla in the retina in 1908 by Mikito Takayasu, a Japanese ophthalmologist at Kanazawa University [5]. The impaired vision of this patient was described as "a case of peculiar changes in the central retinal vessels" [5]. In the same year, Onishi and Kagoshima presented similar cases and mentioned that the pulse became non-palpable

in the radial arteries of the patients [6]. Yasuzo Shinmi coined the term “Takayasu’s arteritis” for the first time in 1929 [7]. In the natural course of TAK, the patient experiences cycles of active and remission phases that reflect different inflammatory states of the arterial lesions [3,8]. Later in 1990, the classification criteria were published by the American College of Rheumatology (ACR criteria) and the proposed name “Takayasu’s arteritis” was accepted worldwide [9].

According to the epidemiological data, the prevalence of TAK is highly gender-biased. It predominantly occurs in adolescent girls and young women between the age of 10 and 30 years, with the female-to-male ratio of 2.1:1 in India [10,11]. TAK is associated with >35% of mortality rate among children of both sexes [12]. Approximately 2/1,000,000 people per year suffer from TAK [10]. Major geographical variation in the prevalence of TAK is observed in Japan, China, India, and other Asian countries [13].

Ample number of experimental and clinical studies have been conducted in the past years but the etiopathogenesis of TAK still remains enigmatic. Indian and Japanese workers suggested TAK as a possible outcome of hypersensitivity to *Mycobacterium tuberculosis* with a likelihood of positive tuberculin skin test in TAK patients [14,15]. Various markers and immunogenic components that interlink TAK with tuberculosis have been identified. However, both TAK and tuberculosis presented weak association according to the previous studies [14-16].

Besides, Sagar *et al.* tested blast transformation to various antigens in TAK patients and reported a significant blast transformation by purified human aortic antigen, implying the role of autoimmunity in the pathogenesis of TAK [17]. However, the findings obtained from a series of experimental and histopathological studies in this direction suggested that cell-mediated immunity, rather than humoral autoimmune mechanisms, may play a role in TAK pathophysiology.

To summarize the etiopathogenesis of TAK, the onset of TAK may occur due to the exposure of an unknown antigen that may lead to an immune response targeting the arterial vessel wall. The association between TAK and human immune response genes, including HLA genes was

studied, and it was believed that HLA molecules have a significant role in the pathogenesis of the disease [18,19]. So far, HLA-B*52 is the only HLA allele that shows the consistent association with TAK. Numerous cohort studies have been carried out in various ethnic groups and the findings showed that the prevalence of TAK is directly proportional to the frequency of HLA-B*52 in the population. The association between TAK and HLA-B*52 frequency was confirmed in a study by Sahin *et al.* that screened 330 Turkish patients with TAK for the presence of HLA-B*52 [20]. In addition, the presence of HLA-B*52 was found to be decreased in late-onset patients, aged >40 years and angiographic type I disease patients with limited aortic involvement (ACR criteria) [9,20]. This well-recognized association has also been reported in Japanese, Korean, Thai, Indian, and European-American populations. Moreover, the association between HLA-B*52 and TAK is highly based on the TAK clinical features, including aortic regurgitation, early age onset, congestive heart failure, and non-type I disease with limited aortic involvement, which makes TAK diagnosis cumbersome. In addition to HLA genes, the genetic variants in non-HLA genes encoding pro-inflammatory cytokines and immune response mediators have been reported for their association with TAK progression [20].

Pathophysiologically and histopathologically, the earliest changes in TAK consist of a granulomatous inflammation and thickening in the adventitia, followed by cellular infiltration of smooth muscles cells and elastin in the tunica media of the affected arterial vessel wall, leading to pathogenic T-lymphocyte response [3,21,22]. TAK may lead to stenosis, blockages, thrombosis, and aneurysms. TAK is a persistently active vasculitis disease, but may allow silent damage accrual [23]. The clinical manifestations of TAK are dependent on two stages of the disease – systemic phase and occlusive phase. In systemic phase which is the first stage of active inflammatory illness, several symptoms such as fatigue, unintended weight loss, aches, and pains, or mild fever may occur. Most patients show elevations in the erythrocyte sedimentation rate (ESR) during this phase. The occlusive phase is succeeded by the systemic phase. During

the second stage of pulseless phase, decreased pulse, high blood pressure, anemia, chest pains, bruits, claudication, shortness of breath, or memory problems may be visualized as the major signs of TAK due to narrowing of affected arteries [3,10,23-25]. The effective treatment of TAK lies with timely recognition of the symptoms and a rapid diagnosis of the disease to prevent the development of obstructive lesions [24].

Attaining proper diagnosis of TAK is a major milestone due to overlapping clinical and pathological features, and lack of definitive evidence of the disease. Thus, the diagnostic and classification criteria are established for the identification of systemic vasculitis and are useful in clinical practice. These criteria help distinguish the TAK patients from healthy individuals and patients with similar conditions, and also rule out the different forms of vasculitis or diseases that resemble TAK, including giant cell vasculitis. Depending on different sets of diagnostic classifications, various TAK classification criteria have been proposed, which are summarized as:

1.1 Ishikawa diagnostic criteria (1988)

Ishikawa diagnostic criteria are the most widely used criteria for the diagnosis of TAK. It was first developed on the basis of observation in 108 Japanese patients with TAK. The criteria are based on three major and ten minor factors along with proposed angiography imaging technique to confirm the involvement of large vessel [25]. The major factors of proposed criteria include <40 years of age, presentation of signs, and symptoms of 1-month duration and lesions in the left and right mid-subclavian artery. On the other hand, the minor factors include high ESR, hypertension, tenderness, and different arterial lesions. The criterion was later modified by Sharma *et al.* (1995) – to familiarize in Indian patients with TAK, resulted in 92.5% sensitivity and 95% specificity which were higher than the original Ishikawa's criteria, underscoring the usefulness of the modified criteria for under-diagnosed TAK patient [26].

1.2 ACR classification criteria (1990)

ACR classification criteria were developed specifically for adult TAK patients to differentiate TAK from other forms of vasculitis. The

classification was based on the observations obtained by comparing 63 TAK patients and 744 patients suffering from other vasculitis. The six chosen criteria for the traditional classification of TAK were based on the demographic, historical and physical examination. The sole demographic criterion was onset of the disease at age of <40 years and the historical criterion include claudication of the extremities. Three findings based on the physical examination include decreased pulse, difference in systolic blood pressure of >10 mm Hg between the arms, and the presence of bruits over one or both subclavian arteries and abdominal arteries. The sixth criterion was arteriographic evidence of narrowing or occlusion of aorta and its branches. Classification based on any three out of the six criteria demonstrated 90.5% sensitivity and 97.8% specificity. Hence, these suggested factors are recommended as diagnostic criteria [9].

1.3 EULAR/PRINTO/PRES criteria (2005)

The European League Against Rheumatism (EULAR)/the Pediatric Rheumatology European Society (PRES)/the Pediatric Rheumatology International Trials Organization (PRINTO) (EULAR/PRINTO/PRES) classification criteria were developed for identifying childhood TAK in patients of <18 years of age. The mandatory criterion of this classification involves angiographic abnormality of the aorta and its branches along with one of the factors such as hypertension, increase in systolic blood pressure of >10 mm Hg in all four limbs, the presence of bruits, claudication due to physical activity, and increased acute phase reactants (ESR and C-reactive protein [CRP]) [27,28].

2 Concept of point-of-care testing (POCT)

POCT is defined as a medical diagnostic testing at bedside of the patient, i.e., at the time and place of patient care. POCT is vital for quick and reliable detection of parameters near bedside for diagnosis, assessment, and monitoring of the disease as well as for therapeutics management [29]. Usually, laboratory tests would take hours to days to reveal the test results. The whole process of testing involves collection of samples, sending the sample to the laboratory, performing the test, and analyzing

results. These diagnostic and care protocols are complex and time-consuming, and require essential health information about the patient [30]. In contrast to the conventional laboratory tests, POCTs are simple tests that can be performed in minimal time with minimal discomfort to the patients.

The driving concept behind POCT is to perform the test immediately near the patient to expedite clinical decisions. POCT involves the usage of portable, transportable, and handheld instruments and test kits. Most of the POCT technology systems are membrane-based strips enclosed in a test cassette. These tests are usually cost-effective, less time-consuming, and reliable. The results can be obtained in real time, thereby speeding up processes to obtain diagnosis and prognosis results [29-31].

Ideally, a POCT platform is a mobile device that is placed at the bedside of the patient, and relevant tests can be performed in real time to reduce the interruptions during examination and treatment. POCT provides relevant information needed on bedside, without any delay in sample processing, central laboratory testing procedures, and results analysis [32]. Furthermore, POCT has many advantages, such as the tests can be performed by the same person who is also treating the patient, simple test procedures, low sample volumes required for analysis, and mobility of the equipment [31].

A wide range of POC assays and analyzers have been established so far for the quantitative determination of biomarkers related to the disease. Numerous POCT technologies that help in the diagnosis of various conditions are being used worldwide, such as blood glucose meter, pregnancy detection kit, and urinalysis. [32] These complementary technologies also lend themselves useful to health-conscious people for monitoring and managing their health [31,32]. Hence, POCT becomes instrumental in improving the quality of medical care and aiding effective medical treatments, without causing further delay.

3 Diagnostic techniques and disease assessment of TAK

To date, there is no single test for determining the onset and progression of TAK. Furthermore, the lack of definitive presentation of the disease poses

a challenge to the diagnosis of TAK. The diagnosis of TAK is based on a number of factors, including symptoms, clinical history, physical examination, laboratory testing, and imaging techniques [27].

3.1 Diagnostic techniques of TAK

3.1.1 Physical examination

TAK is referred to as a pulseless disease [1]. Clinical examination includes absence of pulse, high blood pressure, and abnormal sounds of blood through narrowed blood vessels called “bruits” or abnormal pulsation of blood vessels heard using stethoscope.

3.1.2 Blood tests

ESR and CRP assay are the two most valuable non-imaging tests to date used to determine inflammation and onset of the disease [27,33].

3.1.3 Imaging techniques

The diagnosis of TAK is highly based on the evaluation of lesions in the aorta or its major branches by performing the following imaging techniques [27,34]. The advantages and disadvantages of these imaging techniques are listed in **Table 1**.

3.1.3.1 Angiography

Digital subtraction angiography (DSA) technique is a widely used method to evaluate the arterial tree in TAK patients. During angiography, a flexible catheter is inserted into a large artery and a special contrast dye is injected into the bloodstream through the catheter. X-rays are taken as the dye fills the arteries to observe the normal or interrupted flow of blood due to stenosis of a blood vessel. A person with TAK generally presents with several narrowed arteries [27]. This method is considered the best technique for the assessment of vessel lumen but it is invasive. Due to radiation-related complication risks and invasive nature, this method has been replaced by other reliable techniques.

3.1.3.2 Magnetic resonance angiography (MRA)

The accuracy and sensitivity of MRA are comparable to DSA. It is a non-invasive technique and does not require radiation exposure. The radio waves are passed in a strong magnetic field to create the detailed pictures of vessels on a computer [34-36] so that thorough information of the lesions in

Table 1. Advantages and disadvantages of imaging techniques

Imaging techniques	Advantages	Disadvantages
Angiography	Gold standard	<ul style="list-style-type: none"> • Invasive • Expensive • Involving radiation exposure • Time-consuming • Empty stomach and other conditions required • Involving sophisticated equipment that requires complex procedures
MRA	<ul style="list-style-type: none"> • Painless • No radiation exposure 	<ul style="list-style-type: none"> • Expensive • Time consuming process • Involving sophisticated equipment that requires complex procedures • Diminished picture quality due to unrestricted movements of the patient • Inability to capture small vessels
CT angiography	Suitable for the evaluation of anatomic details	<ul style="list-style-type: none"> • Expensive • Involving radiation exposure • Requires intravenous (I/V) contrast • Involving sophisticated equipment that requires complex procedures
PET	Provide valuable information about cellular activity within inflamed arterial wall	<ul style="list-style-type: none"> • Expensive • Involving radiation exposure • Requires sedation for young children. • Involving sophisticated equipment that requires complex procedures
Ultrasonography (POCT device)	<ul style="list-style-type: none"> • No radiation exposure • Painless • Sensitive • Portable 	<ul style="list-style-type: none"> • Images obtained are dependent on the expertise of sonographer

MRA: Magnetic resonance angiography; CT: Computerized tomography; PET: Positron emission tomography

the aorta and complete arterial anatomy, including thickness and edema, can be provided. MRA is better than DSA for monitoring inflammation and disease activity in TAK patients to differentiate active and non-active phase of the disease and lesion development. This technique is extensively used in children nowadays [27].

3.1.3.3 Computerized tomography (CT) angiography

CT angiography is a non-invasive form of angiography that combines computerized analysis of X-ray images with the use of intravenous contrast dye to visualize the structure of the aorta and its major branches. This imaging technique can also monitor blood flow [37]. CT angiography provides better resolution and detailed three-dimensional images of arterial anatomy. Similar to MRA, the specificity and sensitivity of CT angiography are

excellent, and this method can be used to monitor vascular inflammation and disease activity in TAK patients. CT angiography may be used as a substitute of MRA for one-time assessment and diagnostic purpose [27]. The involvement of high radiation exposure is a major drawback of CT angiography, and thus, this technique is not appropriate for follow-up assessments.

3.1.3.4 Positron emission tomography (PET)

PET is a new imaging technique for the assessment and evaluation of TAK. ¹⁸F-fluoro-deoxy-glucose-PET is an example of PET that utilizes a radiotracer for monitoring the disease. PET is a non-invasive technique that determines arterial metabolic activity with lumenography, anatomical abnormalities, and morphological changes in the arterial vessel wall. In PET, it is necessary to inject a radiotracer into an artery to visualize the areas

of decreased blood flow [38]. The TAK patient is exposed to high dose of radiation when this imaging test is performed in combination with CT or magnetic resonance imaging. On the basis of the contrasting reports, this technique is found to be clinically controversial with respect to the specificity, sensitivity, and assessment of TAK disease activity [38].

3.1.3.5 Ultrasonography

Doppler ultrasound is a sophisticated version of the common ultrasound with the ability to produce high-resolution images of the morphology of the arteries. It is a non-invasive technique, and radiation exposure is not required. Doppler ultrasound can also be used to detect subtle changes in these arteries, inflammatory or non-inflammatory stages, thrombosis, and aneurysms [39]. It is a valuable technique for the follow-up assessments of TAK disease. It is important to note that the quality of results generated using this technique is operator-dependent, and it is also unable to assess disease activity [40].

3.2 Assessment of disease activity

Characteristic malformations of blood vessels that occur in advanced cases of TAK can be detected by imaging techniques [34-39]. However, accurate methods of monitoring the disease activity in TAK patients are lacking. At present, no gold standard methods are present to monitor the disease activity of TAK. Thus, physicians and health-care personnel have to rely on a combination of clinical features, the presence of signs and symptoms, blood-based inflammatory markers, any vascular complaints, and results of imaging modalities to estimate disease activity of TAK. To distinguish the active and non-active phase of the disease and assess disease activity, numerous approaches have been proposed [23-27,41]:

3.2.1 US National Institute of Health (NIH) approach

The US NIH has proposed an approach for the assessment of disease activity in adult TAK patients which one of the most commonly adopted approach worldwide. Still, this approach has not been validated in pediatric TAK patients. The approach is based on three qualitative aspects of the disease

such as clinical features, laboratory parameters, and angiographical examination of large vessel [2,8].

The NIH approach was proposed in 1994 after a prospective study with a follow-up period of 5.3 years on 60 TAK patients. The NIH defined “active disease” as the onset of the disease or worsening of two or more factors, such as constitutional symptoms of systematic phase (i.e., fever, and pain), elevated ESR (an acute phase reactant), occlusive phase symptoms (bruits, claudication, etc.), and imaging diagnostic examination for new vesicular lesion [10].

3.2.2 Birmingham vasculitis activity score (BVAS)

BVAS is considered as a validated approach for the assessment of TAK disease activity, particularly in small- and medium-vessel vasculitis. This approach has been used in both adult and pediatric TAK patient cohorts. There are three versions of BVAS system and the third version, i.e., BVAS for Wegener’s granulomatosis, is clinically used. The score system comprised 56 items representative of nine organ systems for the assessment of vasculitic manifestations. Nonetheless, this approach underestimates the cardiovascular events and findings, which are the prominent features of TAK. Moreover, it does not include imaging techniques for vessel examination, which is a major drawback [2,23-25].

3.2.3 Disease extent index for TAK (DEI-Tak)

DEI-Tak was proposed in 2005 for the follow-up of TAK patients and this index has also been extended for use in large-vessel vasculitis. This tool is an extension of BVAS and comprised 59 clinical components without involving imaging techniques for the detection of symptoms present in the 6 months before the onset of the disease. This approach was designed to evaluate both disease activity and damage. Regardless of that, it is not able to differentiate active and remission phases of the disease [8,24].

3.2.4 Indian Takayasu clinical activity score (ITAS)

ITAS2010 is the first validated score system that was derived from DEI-Tak approach which assesses disease activity based on the symptoms in the

4 weeks before the onset of the disease. ITAS2010 is a six-organ-based system which is comprised of 44 items in which 33 items are based specifically on cardiovascular symptoms with a maximum score of 51. ITAS2010 is able to grade disease activity and has been validated in adult TAK patients. ITAS-A is a modified version of ITAS2010 that combines the score of ITAS2010 with acute phase reactants (ESR and CRP). ITAS2010 is a very sensitive tool because little changes may result in different results. Several studies based on the ITAS2010 system have been carried out, including cohort study in TAK patients in India, open-label study of mycophenolate mofetil in TAK, and translation and validation of ITAS2010 for the Brazilian Portuguese-speaking TAK patients [27,41].

3.2.5 Pediatric vasculitis activity score (PVAS)

PVAS is also based on BVAS approach. It is a validated tool for the assessment of disease activity among children with primary vasculitis. PVAS is used to assess the onset or worsening of symptoms lasting for at least 4 weeks and persistent for a maximum of 3 months. This score system comprises of nine sections with a total score of 63 [10,41].

3.2.6 Pediatric vasculitis damage index (PVDI)

PVDI is a generic score system developed for the assessment of childhood TAK and is based on adult VDI. This score system considers symptoms present for more than 3 months and disease-related damages [26,41].

Despite the advances in the clinical field, there is still a lack of tool for assessing the onset and progression of TAK to achieve timely diagnosis and effective treatment. In addition, lack of specific biomarkers or laboratory tests to determine and assess the onset or progression of TAK would also contribute to delayed diagnosis and treatment [42]. The TAK patients need comprehensive disease assessment and treatment plan that involves recognition of the symptoms at the earliest followed by tests and therapeutics (imaging techniques, clinical tests, and therapeutic treatment) [2,42]. Due to the silent behavior of TAK, it is quite difficult to diagnose the onset of disease, not to mention the use of time-consuming detection techniques could delay the diagnosis and worsen the condition. Therefore, in this context, POCT gains relevance

and is required for the management of TAK at the earliest.

4 Challenges to the diagnosis and prognosis of TAK

With the increasing incidence of TAK in youngsters and children, there is an urgent need of POCT for timely diagnosis and treatment of the disease. A previous study by Kerr *et al* (2011) has shown that juveniles with TAK were 4 times more likely to have a delayed diagnosis relative to their adult counterparts [1]. Therefore, early diagnosis and proper treatment in affected individuals are required to improve survival rates, especially for patients with major complications. However, certain characteristics of TAK pose a challenge to the diagnosis and prognosis of TAK.

4.1 Non-specific signs and symptoms

The most common feature of TAK is the perpetual inflammation in a suppressed state in the vasculature, and therefore, shows non-specific symptoms of systemic phase of the illness. The non-specific signs unfortunately lead to a delay in diagnosis for months or even years. Even in case of timely diagnosis, it is difficult to distinguish between the active phase or the stenotic phase of the illness due to their non-specificity. The two phases of the disease may not always be distinct, i.e., TAK patient may show the features of both the phases at a single point of time. Thus, it is imperative to determine disease activity because immunosuppressive treatments are not effective in the late stage of the disease [1-3].

4.2 Uncertainty in disease onset and progression

The management of TAK patients is highly problematic. The onset and progression course of TAK disease remains uncertain due to poor correlation between clinical features, disease activity, and the lack of blood-based biomarkers [1,8-10].

4.3 Silent behavior

The majority of patients do not show any symptoms until complications, including stroke and dilation of aorta with stretching, occur [1,10]. The occurrence of complication is usually the time when a proper

diagnosis is considered necessary. As a result, the silent behavior of TAK causes delayed diagnosis of the disease.

4.4 Paucisymptomatic presentation of the disease

Paucity of specific symptoms makes the disease unrecognized for so long. It is also very difficult to predict the disease activity in such cases [27].

4.5 Similarity with giant cell arteritis (GCA)

Both GCA and TAK are two forms of large vessel vasculitis which affect the aorta and its branches. Both diseases share the common features, including clinical symptoms, systemic inflammation, and aortic abnormalities on imaging. The major difference between GCA and TAK is the age of the affected patients. TAK affects younger patients who are generally <40 years of age, whereas GCA affects older people who are usually >50 years of age [1-3].

4.6 Delayed diagnosis

Delayed diagnosis is associated with worse repercussions [29]. In therapeutics, “time-outcome” relationship is a major limitation. The success of most therapeutic approaches majorly depends on a timely diagnosis [30]. In a recent pediatric classification criteria study, the authors observed that the mean time from the onset of symptoms of TAK disease to its diagnosis was 1.3 ± 1.6 years. Furthermore, Watson *et al.* presented a pediatric case which linked delayed diagnosis with fatal outcome in a 14-year-old male child with vasculitis [43]. This indicates that TAK demands timely attention.

Taking the above-mentioned characteristics into consideration, timely diagnosis is essential for the treatment of TAK. Therefore, POCT for the diagnosis and assessment of TAK in adults and children is very much required.

5 Applications of POCT in TAK

The greatest challenge in the medical field is to identify the risk of an active disease prevailing in the patients. This explains why diagnostic techniques that could help in quick recognition of the disease are essential. The major driver of diagnosis is

the assessment and detection of disease-related markers, generally known as biomarkers in the clinical field [29,30]. Biomarkers are basically defined as the biological parameters or “molecular signatures” in the biological fluids, such as blood and urine that may serve as the indicators or predictors of health and disease [44]. Identifying the best candidate markers as stage-specific biomarkers (onset and progression) may assist the practitioners in designing the best personalized therapeutic modalities. The use of biomarkers, mobile devices (onset and progression), and diagnostic applications that incorporate the concept of POCT for determining the onset and monitoring the progression of TAK is described as follows:

5.1 Biomarkers for determining TAK onset

On the basis of different criteria and approaches proposed for the assessment of TAK, the acute phase reactants, such as ESR and CRP, are advocated as the principal biomarkers of TAK onset. The examination of these biomarkers is important for the determination of the inflammation and onset of the disease [42,44]. These biomarkers can positively correlate with disease activity of TAK.

5.1.1 ESR

The major challenge of TAK is to monitor its disease activity. ESR remains the probable and reliable marker of disease activity. ESR is a measure of the degree of inflammatory activity or acute phase response in the patient's body [42]. A previous study showed that ESR was elevated in almost three quarters of the active TAK patients [27]. However, elevated blood pressure and ESR which are the most common clinical manifestations of TAK are very helpful in diagnosis of TAK because these manifestations are distinctly uncommon in children [43]. Therefore, the physical and clinical examination, including blood pressure, pulse rate, and bruits, along with a POCT device that can measure ESR would be beneficial in the quick diagnosis of the disease.

5.1.2 CRP

CRP is another vital parameter to assess the inflammation and onset of TAK. Several manufactures have developed POCT device for CRP assay as an additional diagnostic tool. For

instance, a portable reader for the measurement of CRP based on a capillary mechanism has been developed by Siemens Healthcare Diagnostics (Munich, Germany) as a POCT device [44]. This device offers high sensitivity and is also able to detect small elevations in CRP levels. Another example is NeoMedica NW-37 protein analyzer (NeoMedica Bioscience Technology, Niš, Serbia) which measures CRP based on immunochromatography principle. The device requires only 5 µl of blood sample obtained from a finger prick, and the result can be obtained in <7 s and the whole procedure can be completed in <3 min. These POCT devices are cost-effective, less time-consuming and precise. POCT-based CRP tests such as Eurolyser CRP assay (Eurolyser Diagnostica, Salzburg, Austria), cobas POC CRP Test (Roche Diagnostics International Ltd., Rotkreuz, Switzerland), QuikRead go CRP (Aidian, Espoo, Finland), Afinion™ CRP (Abbott, Oslo, Norway), and Suresign Finecare CRP (CIGA Healthcare, Ballymena, UK) are already in the market. POCT for CRP is an important tool for the rapid diagnosis of TAK which would help in decision making in primary care considered along with clinical history of the patient [44].

5.2 Progression markers

5.2.1 Interleukin (IL)-6

IL-6 is a well-known pro-inflammatory cytokine that is released near the onset of inflammation, and it correlates well with the progression of TAK [45]. Similar to the manufacturers of POCT-based CRP tests, numerous manufacturers have developed POC assays for IL-6, such as IL-6 assay for Proxim POCT (Proxim Diagnostics Corp, Santa Clara, CA, USA), Elecsys® IL-6 (Roche Diagnostics, Basel, Switzerland), Nori Human IL-6 POCT systems (Genorise Scientific Inc., PA, USA), ADVIA Centaur IL-6 assay (Siemens Healthineers, Erlangen, Germany), etc. These tests are based on various principles such as those in lateral flow immunoassay, and densitometric-based assay. For instance, the Milenia QuickLine IL-6 immunoassay (Milenia Biotec, Gießen, Germany) can be used for the measurement of IL-6 levels that would help in the quick diagnosis of TAK. The underlying principle of this test is based on the binding of IL-6 to the gold particles-conjugated IL-6 antibody. The complexes of IL-6 and its antibodies diffuse

through the membrane coated with secondary antibody. As the fluid overflows, a colored band appears. The color intensity of the band is directly proportional to the levels of IL-6 in the test sample. IL-6 is a promising marker for early diagnosis in TAK patients [42,45,46].

5.2.2 Anti-neutrophil cytoplasmic antibodies (ANCA)

ANCA are autoantibodies produced by the immune system that targets and attacks specific protein within the neutrophils. ANCA-associated vasculitis (AAV) is an autoimmune disease characterized by damage and inflammation in the small vessels. AAV occurs when the small and medium vessels are attacked by the neutrophils that are attached to ANCA. Unlike TAK, AAV is more common in older people. The symptoms also vary depending on the affected organs. Testing kits, including AESKUSLIDES® ANCA (AESKU Diagnostics, Wendelsheim, Germany) and ANCA Vasculitides test (Quest Diagnostics, New Jersey, USA), are used to detect autoantibodies in the blood to determine AAV so as to differentiate between TAK and AAV [47].

5.3 Cell phone-based POC, Fitbit watch, and iWatch

Cell phone-based POC, Fitbit watch (Fitbit, San Francisco, CA, USA), and iWatch (Apple Inc., Cupertino, CA, USA) are some of the most promising technologies for the assessment of basic health parameters, including heart rate, pulse rate, weight body analysis, blood pressure, and record of physical activity. The state-of-art heartbeat sensors are an inbuilt feature of Apple iWatch Series 3 which notifies the user when there is a low or an irregular heart rhythm. These technologies have become popular in POC diagnostics as they are capable of data collection, analysis, and generation of precise results. The testing is based on the sensors which converts the biological signals into electrical signals and does not require any kind of human biological sample.

Xu *et al.* explained the role of and advances in smartphone-based POC diagnostics in public health, environmental monitoring, and food safety analysis [48]. For example, Scully *et al.* developed smartphone-based POC for monitoring various

physiological parameters such as cardiac R-R interval, breathing rate, and blood oxygen saturation from the images of human body, including fingertips, eyes, and skin [49]. In addition to physiological parameters, smartphone-based pupillometer for assessing nervous system functioning, melanoma detection technology [50], assessment of fatigue status using tongue images (Samsung Electronics, Suwon-si, South Korea) [51], spirometer for lung function [52], etc., were also developed. These technologies will change the face of the current health-care practices.

5.4 Point-of-care ultrasonography (POCUS)

POCUS (GE Health care, Chicago, IL, USA) is a portable ultrasonography technique which is used at the patient's bedside. It is a non-invasive and highly reliable imaging-based POCT technique for the detection of TAK. It has the capacity to carry out timely diagnosis, improves the patient care management and accelerates clinical decision making. The major drawback of this technique is that it requires skilled sonographer with high level of expertise [31].

6 Potential biomarkers of TAK

Other potential biomarkers such as matrix metalloproteinases (MMPs), soluble receptor for advanced glycation end products (sRAGE), and IL-18 have also been demonstrated for the link with TAK progression [44-46]. At present, however, there are no POCT devices available for the assessment of these potential biomarkers.

6.1 MMPs

MMPs are widely associated with various inflammatory vascular disorders, and also play a significant role in the pathogenesis of TAK. MMPs belong to a zinc-containing enzyme family that degrades extracellular matrix. The previous studies suggested that MMP-2, MMP-3, and MMP-9 could be the potential biomarkers to predict disease activity and imaging outcomes of TAK. In our laboratory, extensive work has been carried out in this direction that TAK patients demonstrated enhanced expression of MMP-1, MMP-3, and MMP-9 as compared to controls [53]. Consistent with this finding, Matsuyama *et al.* also reported

that MMP-2 could be a diagnostic marker, while MMP-3 and MMP-9 are relevant biomarkers for the assessment of TAK disease activity [54]. These MMPs are recognized first as active participants in the pathophysiology of TAK and later, as diagnostic biomarkers for TAK disease [46,49]. At present, there are no specific POCT devices available for MMPs.

6.2 sRAGE

Receptor for advanced glycation end products (RAGE) is a transmembrane receptor. Soluble form of RAGE is referred to as sRAGE. A growing number of studies have demonstrated decreased levels of sRAGE in a range of diseases. Besides that, Mahajan *et al.* also demonstrated the decreased levels of sRAGE in active and remission phases of TAK, and the association between decreased levels of sRAGE and TAK progression [55]. According to this study, sRAGE may also have a role in arterial stiffness and its related complications. Collectively, sRAGE can be used as a potential biomarker for prediction of TAK in routine management. However, it is necessary to develop POCT devices for the determination of sRAGE levels.

7 Future perspectives

TAK is an idiopathic disease that represents an unpredictable disease pattern. Therefore, the diagnosis and assessment of disease activity are crucial. In general, TAK is assessed with the presence of constitutional symptoms, bruits, acute phase response, and angiographic features. However, there is no single reliable measure for disease assessment. Of note, a "Surrogate Markers Study" is being conducted by the International Network for the Study of Systemic Vasculitides (INSSYS) to identify the proteins and other molecules that indicate ongoing inflammation from the blood samples of patients with vasculitis. The INSSYS includes more than 300 investigators and experts from more than 50 medical centers across the world.

To obtain a confirmed diagnosis, a number of blood-based biomarkers testing along with clinical and physical examination would be a boon to the effective management of TAK [38,39]. There is a clear need of developing a diagnostic plan to achieve rapid diagnosis with a validated set

of outcome measure for TAK for use in clinical practice under such cumbersome circumstances. A series of features are required to be assessed before a diagnosis is confirmed. Ideally, a diagnosis plan based on the physical and clinical examination followed by the assessment of a reference biomarker selected from a number of disease onset markers should be established to improve the detection process. The disease onset and progression may also be confirmed by using POCUS and by calculating ITAS2010 or PVAS score.

As mentioned earlier, various criteria and classification systems for the assessment of disease activity, damage, and clinical outcomes of TAK are currently available. However, it is also imperative to develop and establish tools, criteria system and diagnostic plan for distinguishing GCA and AAV from TAK. Future work should focus on the development of disease-specific tools, biomarkers, or techniques in this regard.

8 Conclusion

TAK is a rare but potentially life-threatening condition which affects young females. Early diagnosis and proper management are imperative to reduce the risk of morbidity and damage accrual. Hypertension, fever, unexplained weight loss, fatigue, or arthralgia associated with vascular-related findings (such as bruits) may help raise the suspicion and prompt imaging investigation like ultrasonography to reach an early diagnosis, which should be made before the occurrence of irreversible changes in the affected arteries. The assessment of the involvement and extent of disease activity is mandatory as part of the management of all patients [27]. The use of POCT techniques in the diagnosis of the disease is quite promising. POCT-based assays of classical inflammatory markers such as ESR and CRP along with clinical history of the patient can be used to achieve timely diagnosis and prognosis determination of TAK disease. Due to the active and remission cycles of this inflammatory disease, the best method to diagnose TAK would be adopting an assessment of multiple biomarkers [1,3,10]. Improved awareness, timely diagnosis and incorporation of effective therapies, as well as improved monitoring of the disease activity and response to therapy, collectively, represent a comprehensive approach to tackling

this debilitating disease that could result in more favorable clinical outcomes.

Acknowledgments

Sakshi Mehta acknowledges University Grants Commission, New Delhi, India, for financial assistance in the form of Senior Research Fellowship.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

- [1] Kerr, G.S.; Hallahan, C.W.; Giordano, J.; Leavitt, R.Y.; Fauci, A.S.; Rottem M, Hoffman, G.S. Takayasu Arteritis. *Ann. Intern. Med.*, **1994**, 120, 919–29.
- [2] Sekiguchi, M.; Suzuki, J. An Overview on Takayasu Arteritis. *Heart Vessels*. **1992**, 7, 6–10.
- [3] Arnaud, L.; Haroche, J.; Mathian, A.; Gorochoy, G.; Amoura, Z. Pathogenesis of Takayasu's Arteritis: A 2011 Update. *Autoimmun. Rev.*, **2011**, 11, 61–7.
- [4] Jennette, J.C.; Falk, R.J.; Andrassy, K.; Bacon, P.A.; Churg, J.; Gross, W.L.; Hagen, E.C.; Hoffman, G.S.; Hunder, G.G.; Kallenberg, C.G. Nomenclature of Systemic Vasculitis. Proposal of an International Consensus Conference. *Arthritis Rheum.*, **1994**, 37, 187–92.
- [5] Takayasu, M. A Case with Peculiar Changes of the Retinal Central Vessels. *Acta Soc. Ophthal. Jpn.*, **1908**, 12, 554–5.
- [6] Numano, F.; Kakuta, T. Takayasu Arteritis-five Doctors in the History of Takayasu Arteritis. *Int. J. Cardiol.*, **1996**, 54(Suppl), S1–10.
- [7] Sinmi, Y. A case of takayasu's arteritis. *Sogo Gannka.*, **1942**, 36, 1404–10.
- [8] Johnston, S.L.; Lock, R.J.; Gompels, M.M. Takayasu Arteritis: A Review. *J. Clin. Pathol.*, **2002**, 55, 481–6.
- [9] Arend, W.P.; Michel, B.A.; Bloch, D.A.; Hunder, G.G.; Calabrese, L.H.; Edworthy, S.M.; Fauci, A.S.; Leavitt, R.Y.; Lie, J.T.; Lightfoot, R.W. Jr., The American College of Rheumatology 1990 Criteria for the Classification of Takayasu Arteritis. *Arthritis Rheumat.*, **1990**, 33(8), 1129–34.
- [10] Jain, S.; Sharma, N.; Singh, S.; Bali, H.K.; Kumar, L.; Sharma, B.K. Takayasu Arteritis in Children and Young Indians. *Int J Cardiol.*, **2000**, 75, S153–7.
- [11] Brunner, J.; Feldman, B.M.; Tyrrell, P.N.; Kuemmerle-Deschner, J.B.; Zimmerhackl, L.B.; Gassner, I.; Benseler, S.M. Takayasu Arteritis in Children and Adolescents. *Rheumatology*, **2010**, 49, 1806–14.
- [12] Cakar, N.; Yalcinkaya, F.; Duzova, A.; Caliskan, S.; Sirin, A.; Oner, A.; Baskin, E.; Bek, K.; Soylu, A.; Fitoz, S.; Bayazit, A.K.; Bircan, Z.; Ozen, S.; Uncu, N.; Ekim, M. Takayasu Arteritis in Children. *J. Rheumatol.*, **2008**, 35, 913–9.
- [13] Moriwaki, R.; Noda, M.; Yajima, M.; Sharma, B.K.; Numano, F. Clinical Manifestations of Takayasu Arteritis in India and Japan New Classification of Angiographic Findings. *Angiology*, **1997**, 48, 369–79.
- [14] Kinare, S.G. Aortitis in Early Life in India and its Association with Tuberculosis. *J. Pathol.*, **1970**, 1, 69–76.
- [15] Pantell, R.H.; Goodman, B.W. Takayasu's Arteritis: The Relationship with Tuberculosis. *Pediatric*, **1981**, 67, 84–8.
- [16] Chogle, A.R.; Shah, D.A.; Cerejo, C. Analysis of Evidence to Determine the Link between Takayasu's Arteritis and Tuberculosis.

- Ind. J. Rheumat., **2015**, 10, 2–9.
- [17] Sagar, S.; Ganguly, N.K.; Koicha, M.; Sharma, B.K. Immunopathogenesis of Takayasu Arteritis. *Heart Vessels*, **1992**, 7, 85–90.
- [18] Yoshida, M.; Kimura, A.; Katsuragi, K.; Numano, F.; Sasazuki, T. DNA Typing of HLA-B Gene in Takayasu's Arteritis. *Tissue Antigens*, **1993**, 42, 87–90.
- [19] Terao, C.; Yoshifuji, H.; Ohmura, K.; Murakami, K.; Kawabata, D.; Yurugi, K.; Tazaki, J.; Kinoshita, H.; Kimura, A.; Akizuki, M.; Kawaguchi, Y.; Yamanaka, H.; Miura, Y.; Maekawa, T.; Saji, H.; Mimori, T.; Matsuda, F. Association of Takayasu Arteritis with HLA-B 67:01 and Two Amino Acids in HLA-B Protein. *Rheumatology*, **2013**, 52, 1769–74.
- [20] Sahin, Z.; Bicakcigil, M.; Aksu, K.; Kamali, S.; Akar, S.; Onen, F.; Karadag, O.; Ozbalkan, Z.; Ates, A.; Te Ozer, H.; Yilmaz, V. Takayasu's Arteritis is Associated with HLA-B*52, but not with HLA-B*51, in Turkey. *Arthritis Res. Ther.*, **2012**, 14, R27.
- [21] Noris, M. Pathogenesis of Takayasu's Arteritis. *J. Nephrol.*, **2001**, 14, 506–13.
- [22] Inder, S.J.; Bobryshev, Y.V.; Cherian, S.M.; Wang, A.Y.; Lord, R.S.; Masuda, K.; Yutani, C. Immunophenotypic Analysis of the Aortic Wall in Takayasu's Arteritis: Involvement of Lymphocytes, Dendritic Cells and Granulocytes in Immuno-inflammatory Reactions. *Cardiovasc. Surg.*, **2000**, 8, 141–8.
- [23] Kim, E.S.; Beckman, J. Takayasu Arteritis: Challenges in Diagnosis and Management. *Heart*, **2018**, 104, 558–65.
- [24] Mason, J.C. Takayasu Arteritis Advances in Diagnosis and Management. *Nat. Rev. Rheumatol.*, **2010**, 6, 406–15.
- [25] Ishikawa, K. Diagnostic Approach and Proposed Criteria for the Clinical Diagnosis of Takayasu's Arteriopathy. *J. Am. Coll. Cardiol.*, **1988**, 12, 964–72.
- [26] Sharma, B.K.; Jain, S.; Suri, S.; Numano, F. Diagnostic Criteria for Takayasu Arteritis. *Int. J. Cardiol.*, **1996**, 54(Suppl), S141–7.
- [27] Russo, R.A.; Katsicas, M.M. Takayasu Arteritis. *Front. Pediatr.*, **2018**, 6, 265.
- [28] DeJaco, C.; Ramiro, S.; Duftner, C.; Besson, F.L.; Bley, T.A.; Blockmans, D.; Cimmino, M.A.; Clark, E.; Dasgupta, B. EULAR Recommendations for the Use of Imaging in Large Vessel Vasculitis in Clinical Practice. *Ann. Rheum. Dis.*, **2018**, 77, 636–43.
- [29] Price, C.P. Point-of-care Testing Impact on Medical Outcomes. *Clin. Lab. Med.*, **2001**, 45, 1104–21.
- [30] O'Kane, M. Point of Care Testing Current and Emerging Perspectives. *Point Care J. Near Patient Test. Technol.*, **2014**, 31, 1–5.
- [31] Giallams, S.; St John, A.; Laurence, C.O. Point-of-care Testing for Patients with Diabetes, Hyperlipidaemia or Coagulation Disorders in the General Practice Setting: A Systematic Review. *Fam. Pract.*, **2010**, 27, 17–24.
- [32] Vashist, S.K.; Luppia, P.B.; Yeo, L.Y.; Ozcan, A.; Luong, J.H. Emerging Technologies for Next-Generation Point-of-Care Testing. *Trends Biotechnol.*, **2015**, 33, 692–705.
- [33] Alibaz-Oner, F.; Yentür, S.P.; Saruhan, Park YB, Lee SK, Direskeneli G, Direskeneli H. Serum Cytokine Profiles in Takayasu's Arteritis: Search for Biomarkers. *Clin. Exp. Rheumatol.*, **2015**, 33(2 Suppl 89), S32–5.
- [34] Barta, L.; Kanji, T.; Malette, J.; Pagnoux, C. Imaging Modalities for the Diagnosis and Disease Activity Assessment of Takayasu's Arteritis: A Systematic Review and Meta-analysis. *Autoimmune. Rev.*, **2018**, 17, 175–87.
- [35] Choe, Y.H.; Han, B.K.; Koh, E.M.; Kim, D.K.; Do, Y.S.; Lee, W.R. Takayasu's Arteritis: Assessment of Disease Activity with Contrast Enhanced MRI Imaging. *Am. J. Roentgenol.*, **2000**, 175, 205–11.
- [36] Tso, E.; Flamm, S.D.; White, R.D.; Schwartzman, P.R.; Mascha, E.; Hoffman, G.S. Takayasu Arteritis: Utility and Limitations of Magnetic Resonance Imaging in Diagnosis and Treatment. *Arthritis Rheum.*, **2002**, 46, 1634–42.
- [37] Yamada, I.; Nakagawa, T.; Himeno, Y.; Numano, F.; Shibuya, H. Takayasu Arteritis: Evaluation of the Thoracic Aorta with CT Angiography. *Radiology*, **1998**, 209, 103–9.
- [38] Arnaud, L.; Naroche, J.; Malek, Z.; Archambaud, F.; Gambotti, L.; Grimon, G.; Kas, A.; Costedoat-Chalumeau, N.; Cacoub, P. Is (18) F-Fluorodeoxyglucose Positron Emission Tomography Scanning a Reliable way to Assess Disease Activity in Takayasu Arteritis? *Arthritis Rheum.*, **2009**, 60, 1193–200.
- [39] Schmidt, W. Role of Ultrasound in the Understanding and Management of Vasculitis. *Ther. Adv. Musculoskelet. Dis.*, **2014**, 6, 39–47.
- [40] Andrews, J.; Al-Nahhas, A.; Pennell, D.J.; Hossain, M.S.; Davies, K.A.; Haskard, D.O.; Mason, J.C. Non-invasive Imaging in the Diagnosis and Management of Takayasu's Arteritis. *Ann. Rheum. Dis.*, **2004**, 63, 995–1000.
- [41] Fritsch, S.; Copes, R.M.; Savioli, B.; Aguiar, M.F.; Ciconelli, R.M.; Azevedo, V.F.; de Souza AW. Translation and Validation of the Indian Takayasu Clinical Activity Score (ITAS2010) for the Brazilian Portuguese Language. *Adv. Rheumatol.*, **2019**, 59, 43.
- [42] Park, M.C.; Lee, S.W.; Park, Y.B.; Lee, S.K. Serum Cytokine Profiles and their Correlations with Disease Activity in Takayasu's Arteritis. *Rheumatology*, **2006**, 45, 545–8.
- [43] Watson, L.; Brogan, P.; Peart, I.; Landes, C.; Barnes, N.; Clear, G. Diagnosis and Assessment of Disease Activity in Takayasu Arteritis: A Childhood Case Illustrating the Challenge. *Case Rep. Rheumatol.*, **2014**, 2014, 603171.
- [44] Maksimowicz-McKinnon, K.; Bhatt, D.L.; Calabresse, L.H. Recent Advances in Vascular Inflammation: C-reactive Protein and other Inflammatory Biomarkers. *Curr. Opin. Rheumatol.*, **2004**, 16, 18–24.
- [45] Kong, X.; Sun, Y.; Ma, L.; Chen, H.; Wei, L.; Wu, W. The Critical Role of IL 6 in the Pathogenesis of Takayasu Arteritis. *Clin. Exp. Rheumatol.*, **2016**, 34(Suppl 97):S21–7.
- [46] Sun, Y.; Ma, L.; Yan, F.; Liu, H.; Ding, Y.; Hou, J.; Jiang, L. MMP-9 and IL-6 are Potential Biomarkers for Disease Activity in Takayasu's Arteritis. *Int. J. Cardiol.*, **2012**, 156, 236–8.
- [47] Seo, P.; Stone, J.H. The Antineutrophil Cytoplasmic Antibody-associated vasculitides. *Am. J. Med.*, **2004**, 117, 39–50.
- [48] Xu, X.; Akay, A.; Wei, H.; Wang, S.; Murphy, B.P.; Erlandsson, B.E.; Li, X.; Lee, W.G. Advances in smartphone-based Point-of Care Diagnostics. *Proc. IEEE*, **2015**, 103, 236–48.
- [49] Scully, G.C.; Lee, J.; Meyer, J.; Gorbach, A.M.; Fraser, D.G.; Mendelson, Y.; Chon, K.H. Physiological Parameter Monitoring from Optical Recordings with a Mobile Phone. *IEEE Trans. Biomed. Eng.*, **2012**, 59, 303–6.
- [50] Wadhawan, T.; Situ, N.; Rui, H.; Lancaster, K.; Yuan, X.; Zouridakis, G. Implementation of the 7-point Checklist for Melanoma Detection on Smart Handheld Devices. *Proc. IEEE Eng. Med. Biol. Soc.*, **2011**, 2011, 3180–3.
- [51] Kim, T.S.; Yoon, G.; Lee, J.; Shin, S. Method of Extracting Region of Interest from Tongue Image and Health Monitoring Method and Apparatus Using the Tongue Image. *Europe*, **2004**, 2004, EP1450287A2.
- [52] Larson, E.C.; Goel, M.; Boriello, G.; Heltshe, S.; Rosenfeld, M.; Patel, S.N. SpiroSmart: Using a Microphone to Measure Lung Function on a Mobile Phone. *Proc. ACM Conf Ubiquitous Comput.*, **2012**, 1, 280–9.
- [53] Wu, G.; Mahajan, N.; Dhawan, V. Acknowledged Signatures of Matrix Metalloproteinases in Takayasu's Arteritis. *Biomed. Res. Int.*, **2014**, 2014, 827105.
- [54] Matsuyama, A.; Sakai, N.; Ishigami, M.; Hiraoka, H.; Kashine, S.; Hirata, A.; Nakamura, T.; Yamashita, S.; Matsuzawa, Y. Matrix Metalloproteinases as Novel Disease Markers in Takayasu Arteritis. *Circulation*, **2003**, 108, 1469–73.
- [55] Mahajan, N.; Dhawan, V.; Sangvan, S.; Jain, S. Serum Levels of Soluble Receptor for Advanced Glycation end Product (sRAGE) in Takayasu's Arteritis. *Int. J. Cardiol.*, **2010**, 145(3), 589–91.