Ask anyone in the general population what they know about having a “blood test” and the likely response will be that they believe the test was performed to establish their blood group such as Group O, A, B, or AB. If the question is asked of a patient with Paget’s Disease then the most likely answer would be that the test was performed to measure alkaline phosphatase. In practice, blood grouping is a test rarely performed routinely, but is commonly requested prior to any operation or a blood transfusion. However, alkaline phosphatase is very important to help make the diagnosis of Paget’s disease and help guide treatment.

“Routine” Blood Tests
Symptoms that suggest Paget’s disease as a possible diagnosis include bone or joint pain, deformity or increasing size of a bone, fracture and deafness. “Routine” blood tests give information about the major organs in the body that in turn can help to identify causes of these symptoms. These tests are usually grouped together to reflect organ function such as U&Es (kidney function), LFTs (Liver function), Bone profile (calcium and bone metabolism), and FBC (red blood cell and white cell number/function). Each of these blood tests will measure several ions, proteins, peptides, other small molecules and cells and can indicate if one or more of the body’s organs are not functioning correctly. It is very often the profile or combination of changes in a number of the measured substances that indicate a problem exists in a particular organ and can help establish the correct diagnosis.

Alkaline Phosphatase
Alkaline phosphatase, sometimes shortened to ALP is a special type of protein molecule known as an enzyme that can act to remove phosphate groups from molecules throughout the body. It is present in almost every cell within the human body but has a particularly high concentration in certain cells and organs. The highest concentration is seen in specific cells from the liver, bone, intestine, kidney and placenta. When the cells of an organ containing alkaline phosphatase are very active or damaged the alkaline phosphatase is released into the blood stream and can be measured as part of some routine profiles e.g. LFTs or Bone Profile. In most patients with Paget’s disease the osteoblast cells that make bone become more active and subsequently produce higher levels of alkaline phosphatase. Generally, if the disease affects several bones (polyostotic) this will result in a higher alkaline phosphatase level in the blood. If the disease is particularly active and there is very high bone turnover then the alkaline phosphatase increases in blood greater than might be predicted from the amount of bone affected.

It is often obvious from the profile of blood tests that a patient is suffering from Paget’s disease as the alkaline phosphatase is the only abnormal high result observed. This diagnosis can then be confirmed by further tests including an X-ray and/or bone scan. However, some patients may be suffering from several different
diseases, which can complicate interpretation of the test results. For example, liver function may be commonly affected with advancing age and as the liver is a major source of alkaline phosphatase this can lead to high levels in the blood. A routine blood test cannot distinguish between the different sources of alkaline phosphatase but if there is liver damage it is likely that the blood test would show additional abnormalities. It is also possible to perform special tests for the specific bone form of alkaline phosphatase and these tests are used in cases where there is a smaller amount of bone affected by Paget’s disease (monostotic or one bone affected) or where another organ source of alkaline phosphatase may be contributing to the total alkaline phosphatase.

**Treatment and Alkaline Phosphatase**

The commonest and most effective treatments used in Paget’s disease are either intravenous or oral bisphosphonate. Following bisphosphonate treatment there is a marked decrease in bone turnover and a significant reduction in both osteoclast and osteoblast cell activity within the affected bone. Because of this decrease in cell activity, the alkaline phosphatase in blood decreases. A doctor treating a patient with a bisphosphonate can use the decrease in alkaline phosphatase as an indicator that the treatment has been effective. Additionally, if the response in terms of the alkaline phosphatase decrease is not big enough he can give further treatment to attempt to “normalise” the bone turnover. During regular follow up post treatment, the alkaline phosphatase can be measured and if this increases significantly then a further course of treatment given.

**Frequently Asked Questions Regarding Alkaline Phosphatase**

**Is it possible to have a normal alkaline phosphatase when there is active Paget’s disease?**

Not all those with Paget’s disease have an increased alkaline phosphatase, with about 10% of patients presenting with a level within the reference range. This occurs because in the population, enzyme concentrations in blood have a very wide variability in what is considered “normal.” Therefore, a result within the population reference range can be abnormal for someone who normally has a low level of the enzyme circulating in his or her blood. If this occurs, it may be helpful to perform additional tests such as measuring the bone specific alkaline phosphatase. There are also markers of bone activity that can be measured in blood and urine and these can be increased when alkaline phosphatase appears to be normal.

**Will symptoms always improve when alkaline phosphatase falls?**

For the majority of patients the decrease in alkaline phosphatase, following bisphosphonate treatment, is accompanied by an improvement in symptoms but we do know that this does not occur universally. The PRISM study highlighted that this was the case for patients receiving intensive bisphosphonate therapy compared to symptomatic therapy. This could be because some of the symptoms are not related to Paget’s Disease but are a consequence of the disease for example arthritis which may require alternative treatment. Zoledronate is the most potent bisphosphonate now available, and studies have shown that this results in a better symptomatic response compared to pamidronate or risedronate. The findings of another study, PRISM-EZ may help confirm similar results with improved quality of life scores in patients receiving zoledronate treatment. In some patients it is possible that the disease has progressed too far before treatment has been initiated to make a big difference in symptoms emphasising the importance of early identification and treatment.
Why do reference ranges for alkaline phosphatase vary throughout the UK?
Different laboratories use different commercial methods to measure the activity of alkaline phosphatase. Measurement is also affected by many factors including temperature, amount and type of molecule used and finally interpretation depends on the population used to define the reference range. While biochemistry laboratories, across the UK, have been working very hard to harmonize results for many of the tests they perform, there are inherent differences in certain tests, like alkaline phosphatase, that at present cannot be changed. Ideally, following diagnosis, repeat alkaline phosphatase should be measured using the same method. If this is impossible the result needs to be calculated compared to the reference range for different methods of analysis used.

Conclusion
Blood tests, along with clinical assessment, x-ray and bone scan, are important in helping make the diagnosis of Paget’s disease. They are also useful in measuring response to treatment and can help to guide the need for further therapy. Alkaline phosphatase is one of the commonest tests performed with other blood and urine tests used to give a clear indication of bone and organ function.

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