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Big data analysis reveals the existence of seasonal pseudohyperkalaemia even in temperate climates

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ABSTRACT

Background: Seasonal pseudohyperkalaemia has been described in colder northern hemisphere countries. The lower temperatures may inhibit red cell Na-K-ATPase allowing the efflux of potassium and higher measured levels. It has not been described in warmer subtropical climates.

Aims: The aim was to determine if seasonal variation in serum potassium occurred in a temperate climate.

Methods: We conducted a retrospective review of serum potassium results over two years in two South African provinces with different microclimates and seasonal temperatures. The study included patient samples from surrounding clinics and hospitals in Pretoria, Gauteng province, and in Durban, KwaZulu-Natal province, South Africa. Average temperature ranges were obtained from the South African weather service from the same period (June 2015–June 2017).

Results: A total of 91,420 results were analysed and we found a statistically significant difference between the January (summer) and June (winter) serum potassium levels ($p < .0001$). These results demonstrate that the winter months in South Africa are associated with significantly higher measured potassium results.

Conclusion: Seasonal pseudohyperkalaemia may be more widespread than realized and can occur in more temperate climates and laboratories should take the appropriate action when transporting samples as this could influence interpretation and clinical management.

1. Introduction

Artefactual or spurious hypo- and hyperkalaemia are well-known analytic problems in clinical chemistry. Factitious hyperkalaemia can arise from many causes including bad phlebotomy technique, thrombocytosis,leucocytosis and delayed separation of whole blood samples [1–3]. In patients with a leukaemic blast crisis there can be time-dependent transport of potassium into the leukaemic cells after a blood sample is taken [1]. Additionally, use of myelopoietic growth factors after chemotherapy can lead to rapid potassium uptake by new cells. In these settings it is important to process the samples as quickly as possible [3]. Clinical laboratories need to ensure that potassium results are subjected to stringent quality control. The most common cause of spurious or (pseudo) hyperkalaemia is observed daily in many laboratories when elevated [1] serum potassium concentrations, usually arising from haemolysis, are incongruent with the clinical picture [2].

The ambient temperature is also an important factor that contributes to spurious hyper- and hypokalaemia [4–6]. Previous studies in colder climates have revealed a significant inverse correlation between daily temperature and mean potassium concentration [4–6]. Higher daily temperatures increase the incidence of hypokalaemia in the summer. On the other hand, in winter there is an increased incidence of hyperkalaemia [4–6]. With the exception of a few reports from the United Kingdom, it is not known how prevalent this problem is in different countries and laboratories [4–6]. In a temperate to subtropical climatic region, such as in South Africa where temperature extremes are not characteristic in comparison with the United Kingdom, it was not clear as to how common this phenomenon is. This study was conducted in two provincial regions: Durban, KwaZulu-Natal and Pretoria, Gauteng in South Africa. Durban, located on the Indian ocean, boasts an average of 320 days of sunshine a year. Temperatures range from 16 to 25 °C in winter. During the summer months temperatures range from 23

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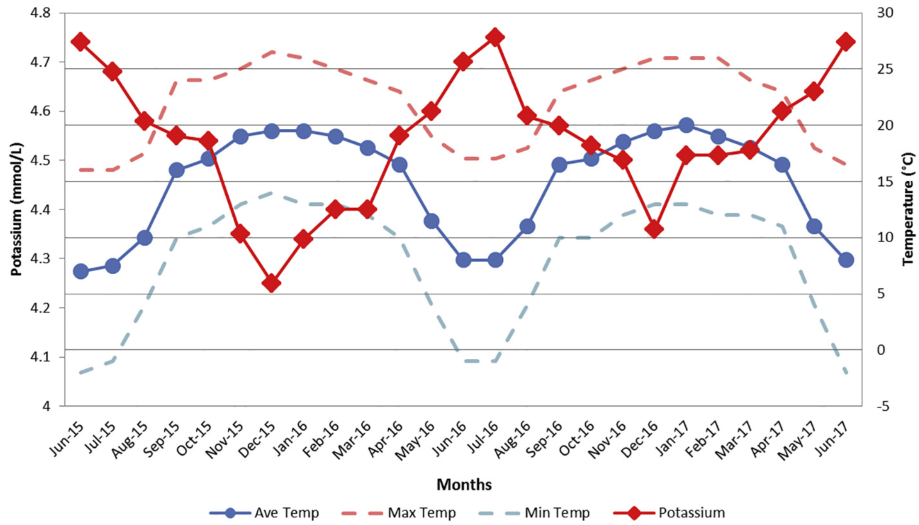

Fig. 1. Seasonal variation in average potassium results over a 2 year period (Gauteng province) $*p < .0001$. Mean average serum potassium results are shown along with the minimum, maximum and average temperatures.

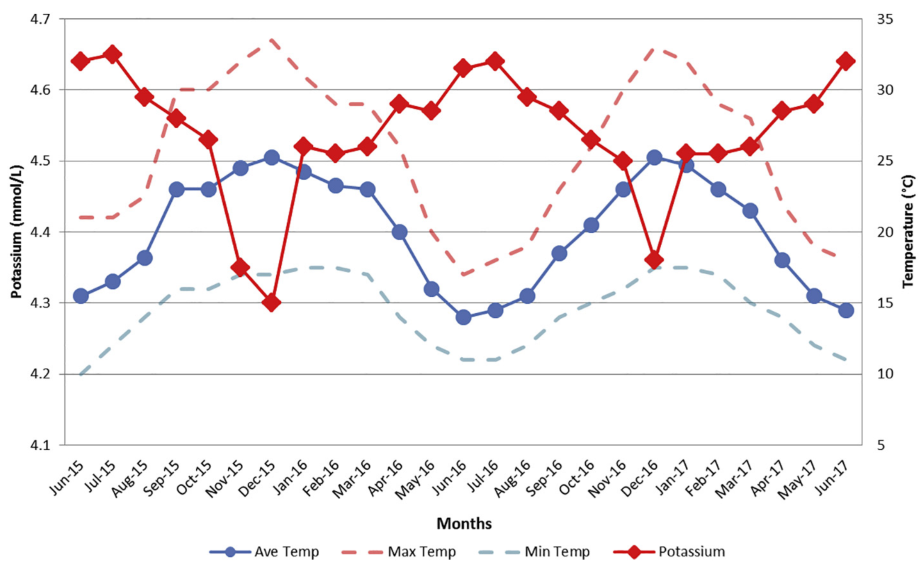

Fig. 2. Seasonal variation in average potassium results over a 2 year period (KwaZulu-Natal province) $*p < .0001$. Mean average serum potassium results are shown along with the minimum, maximum and average temperatures.

to 33 °C. January is generally Durban's hottest month, with an average daily temperature of ± 32 °C. Pretoria, Gauteng has a milder climate and January is the hottest month in Pretoria with an average temperature of 24 °C and the coldest is June at 12 °C. In mid-winter, Pretoria has high average daytime temperatures of approximately 20° C and cooler night climates when the temperature can drop to 5 °C.

The aim of this study was therefore to determine whether "big data" analysis would reveal seasonal changes in the measured potassium levels at diagnostic laboratories in the temperate to subtropical climates found in South Africa which has four distinctive climatic regions with different microclimates.

2. Methods

The study was approved by the University of Pretoria Faculty of Health Sciences Research Ethics Committee application number 544/2017. Data was obtained from two provincial regions with different climates i.e. Gauteng province and KwaZulu-Natal. We extracted 91,420 serum potassium results over a 2 year period from June 2015–June 2017. All haemolysed samples were excluded from the analysis. 80,561 results were from samples sent to the public sector teaching hospital (University of Pretoria Steve Biko academic hospital). The samples received included those from inpatients at the local university teaching hospital and the surrounding clinics and hospitals. The average daily temperature recordings were obtained from the South African weather service. All haemolysed specimens were excluded from the study. Approximately 10,859 results were from the KwaZulu-Natal region from specimens sent to a private sector laboratory. All samples were transported to the laboratory at ambient temperature prior to analysis and analysed within 4 h.

All serum potassiums were analysed on a Beckman Coulter DXC800 (Gauteng) or DXC600 (KwaZulu-Natal) (CV < 5%). Samples had been collected in BD specimen tubes and serum potassium was measured using ion selective electrodes. The laboratories were air conditioned throughout the year and the analysers did not exceed their manufacturer-specified working temperature range during the study period. The local reference range for serum potassium is 3.5–5.1 mmol/L. The mean potassium result and the mean daily temperature was compared during each month of the year. Data was analysed using Microsoft excel and Graphpad Prism (La Jolla, CA, USA) version 4 software. The *t*-test

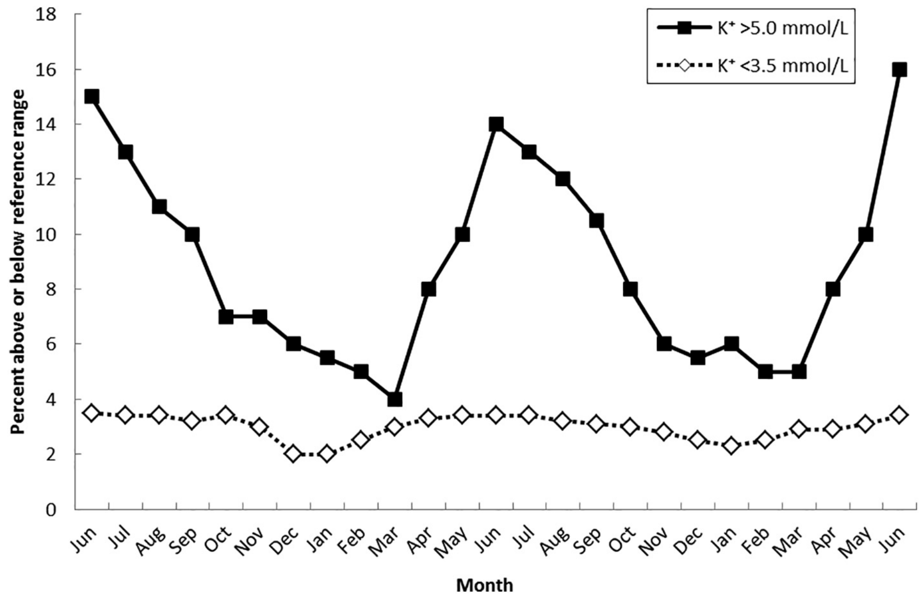

Fig. 3. Percentage of serum potassium results above and below the reference range (Gauteng Province).

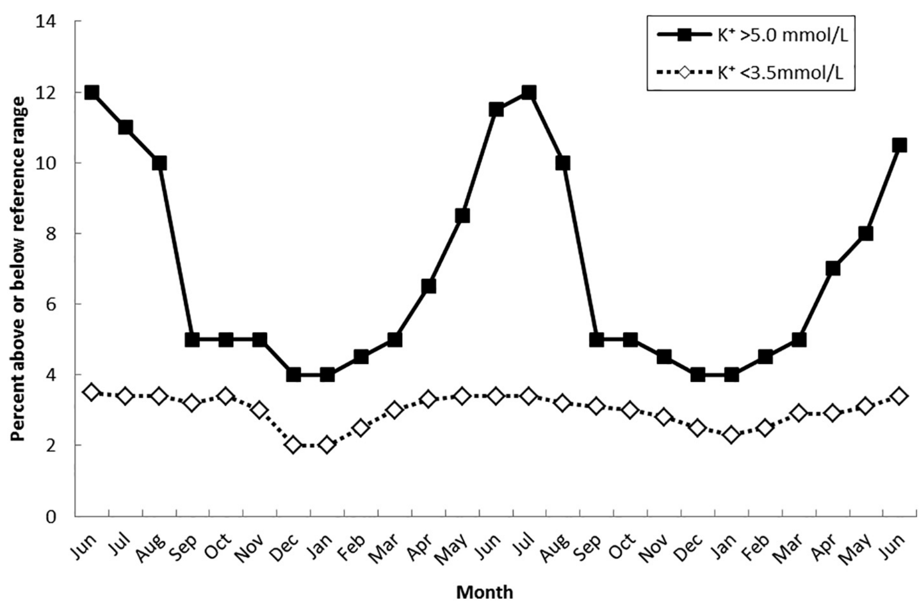

Fig. 4. Percentage of serum potassium results above and below the reference range (KwaZulu-Natal Province).

was used to evaluate the differences between each group and a p value < .05 was considered statistically significant.

3. Results

Fig. 1 shows the average serum potassium for each month of the year in the Gauteng province (June 2015–June 2017). There was a significant increase in serum potassium in the the winter months (May,June,July) when compared to the summer months(Dec,Jan,Feb) in the two year period($p < .0001$). There was no significant difference in serum potassium between the summer months of consecutive years (eg Dec 2015 vs Dec 2016) or the winter months of consecutive years (eg. Jun 2016 vs Jun 2017).

There was an inverse correlation between serum potassium and average temperature. As the temperature dropped in the Southern hemisphere winter months (May,June,July) the average serum potassium increased with the peaks in the winter months, followed by troughs in the warmer summer months, as the average temperature increased.

Fig. 2 shows the results obtained from a laboratory based in the warmer KwaZulu-Natal province over the two year study period. ($p < .0001$).

We also examined the percentage of potassium results above 5.0 mmol/L and below 3.5 mmol/L. From the graphs in Fig. 3 and Fig. 4, it can be observed that the incidence of hyperkalaemia increases to 14% in the months of June, compared to < 6% in December ($p < .05$). This implies that clinically significant hypokalaemia may be masked in the colder winter Southern hemisphere months.

4. Discussion

Previous studies have demonstrated the phenomenon of seasonal factitious changes in serum potassium, particularly in the colder winter months in the United Kingdom [6]. As a result of this phenomenon, many laboratories in the United Kingdom took steps to install centrifuges at primary care sites so that serum could be separated at site

[7,8]. The impact of this was observed as a concurrent reduction in hyperkalaemia improving the quality of potassium results [7,8]. It is not clear how widespread the phenomenon of seasonal changes in potassium are in different countries with different climates across the world.

This current study conducted in two climatic regions of South Africa with slightly different but mild climatic conditions has revealed that the average of the measured serum potassium levels increased significantly with a drop in ambient temperature and this showed cyclical change with the seasons in a temperate climate. The majority of the samples used in this study were inpatient samples and analysis was performed within 4 h in the majority of samples. Potassium levels have been reported to be stable for four to six hours [9–11] indicating that the delay in analysis is unlikely to have influenced the results. Furthermore, in the initial selection of samples, samples that had been delayed for > 6 h were excluded from the analysis.

During the summer months, average serum potassium levels decreased to the lowest levels. Conversely, in the winter months, average serum potassium increased. There was an inverse correlation between average serum potassium levels and monthly ambient temperature. In addition, there was an increase in the incidence of hyperkalaemia as indicated by the percentage of potassium results above the reference ranges. The most likely explanation is that samples are being exposed to the ambient temperature of the season between phlebotomy and analysis in the laboratory. There could also be an issue of the time delay before analysis but it is expected that the incidence and effects of delays would have averaged out over the two years. In this instance, the phenomenon is clearly cyclical and seasonal. The data supports the idea that there is a need to centrifuge samples at the primary phlebotomy site thereby eliminating spurious results. Cooling the blood down below ambient temperature after venepuncture diminishes the Na/K ATPase pump activity thus enhancing leakage out of the cell and falsely increasing serum potassium levels. The role of the Na/K ATPase pump has been demonstrated by the use of oubain to inhibit the pump [6]. There is a need to keep blood at the correct ambient temperature or even perhaps at 37 °C for as long as possible before arrival at the laboratory before processing. However, prolonged incubation of samples at 37 °C will lower the potassium levels and increase the incidence of hypokalaemia [6]. Delays in specimens reaching the laboratory leads to falsely high potassium results especially during the winter months and this study shows that this can be observed in regions with moderate peak winter temperatures unlike those seen in Europe or elsewhere. Interestingly, the lower reference limit for potassium reference ranges tends to be lower in warmer countries [12].

A spuriously high potassium could be detrimental to a patient who has hypokalaemia which could be disguised as normokalaemia because of the spurious elevation. Clinicians and laboratories should therefore take note of how specimens are transported to the laboratory and also the seasonal changes in temperature and the potential effects on potassium results. A clinician may need to be aware that if there is a threshold level of potassium where an upward change caused by a preanalytical variable may lead to potential misdiagnosis of whether there is a hyperkalaemia or not. It is not possible for the laboratory to control all preanalytical variables and the more clinicians are aware of the preanalytical variables, the more accurate the interpretation will be. Other studies have concluded that a temperature-controlled transport medium improved spurious results [6]. The Clinical and Laboratory Standards institute recommends centrifugation within 2 h to maintain the integrity of the sample [13]. This may be difficult to achieve in some settings but centrifugation on site will alleviate the problem significantly [8].

We also compared the age and gender distribution between the groups for the months of June 2015 and January 2016 and did not find any statistical difference (data not shown). Although it is possible that between-patient variation may be a factor, over time the differences in a large dataset will even out as we are considering the mean across a large number of people. Moreover, the phenomenon is strikingly cyclical from year to year, even in the years outside this dataset.

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