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ORIGINAL RESEARCH

Efficacy of oral iron therapy in geophagic women with iron deficiency anaemia residing in Botshabelo, South Africa

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Background: Iron deficiency anaemia is the most commonly encountered form of anaemia in females worldwide. This form of anaemia is, amongst others, associated with geophagia that is defined as the consumption of soil. The two main reasons for the association of geophagia with anaemia are that soil is thought to supplement mineral deficiency and geophagia is seen as a symptom of the anaemia. However, it is hypothesised that soil consumption interferes with iron absorption instead of supplementing it. The first line of therapy for iron deficiency anaemia is oral iron. Therefore, if soil consumption interferes with iron absorption it could interfere with oral iron therapy leading to patients being burdened with symptoms of anaemia as treatment is not effective. The aim of the study was to evaluate the efficacy of oral iron therapy in female participants afflicted with iron deficiency anaemia associated with geophagia.

Methods: In this prospective randomised intervention study, 84 geophagic women with iron deficiency anaemia were divided into two groups. One group continued with soil consumption while the other stopped consumption. Oral iron therapy was administered for ten weeks at increasing therapy doses for both groups. Red cell and iron study parameters were evaluated at different time intervals to ascertain the efficacy of iron replacement therapy.

Results: The group that stopped soil consumption showed a statistically significant change in haemoglobin (9.4 to 10.0 g/dL, $p = 0.029$), mean corpuscular volume (73.6 to 75.7 fl), mean corpuscular haemoglobin (23.7 to 24.6 pg), serum iron (22.5 to 28 µg/dL, $p < 0.001$, transferrin saturation (4.8 to 6.9%, $p < 0.001$) and total iron-binding capacity (467 to 441 µg/L, $p = 0.001$). These findings were contrary to the group that continued with consumption, where the statistical changes were only observed for the iron study parameters (serum iron: 21 to 28 µg/dL, $p = 0.038$; transferrin saturation: 4.3 to 6.9%, $p = 0.011$; total iron-binding capacity: 496 to 421 µg/L, $p = 0.002$). Nevertheless, the changes for both groups were clinically insignificant. Oral iron therapy did not correct the anaemia in geophagic females of both groups, this could be explained by two hypotheses where soil affected the gastrointestinal lining and soil directly interfered with therapy iron absorption. This is evidenced by the group that continued with consumption showing fewer changes than the group that abstained from soil consumption. These results were consistent with a case study where oral iron therapy was implemented.

Conclusion: Oral iron therapy was not effective in geophagia cases of iron deficiency anaemia.

Keywords: oral iron therapy, ferrimed, ferritin, geophagia, haemoglobin, transferrin saturation

Introduction

The deliberate consumption of soil, also known as geophagia, is mostly seen as a practice of marginal oddity. However, the practice is found throughout history.[1] It is observed in many individuals and it has a peculiar multifactorial origin.[2-9] Geophagia is derived from the Greek words geo- meaning earth and phagia- meaning eat.[10] Consequently, geophagia can be described as the deliberate habitual consumption of soil/clay that is considered developmentally inappropriate.[11-13] In order for persons to be diagnosed as geophagic, they must have consumed earthly substances continuously for more than one month.[14] Geophagic practice has been described worldwide and it is widespread.[1,5,15-27] From a plethora of studies, the percentage of people practising geophagia has been estimated to be anything from 5% to 85%, depending on the specific studied population.[28-32] The challenge for the current study was the paucity of information on the exact prevalence of geophagia on the study's target population, non-pregnant females. Moreover, it has been postulated that geophagia is more prevalent in sub-Saharan Africa.[32-33] Geophagia has been reported among women and children in southern Africa[5] particularly in South Africa.[25,27,34] It is also said to be more common in people of African descent,[32] especially women with iron deficiency anaemia.[7,8,27-30,35,36]

Iron deficiency anaemia (IDA) is the most common cause of anaemia worldwide.[37-39] Globally, over two billion people are affected by iron deficiency.[40] Furthermore, in the high-risk group composed of childbearing age females, a prevalence of 30% for IDA is noted for non-industrialised countries.[40] An overall estimate of between 15–20% for anaemia and 7–15% for IDA in non-pregnant women was reported by various studies conducted in South Africa.[41-44] IDA results when the net balance of iron absorption and loss is tilted towards iron loss. IDA in association with geophagia is commonly encountered in women of childbearing age as a result of menstrual blood loss

and pregnancy secondary to supply of iron to the developing foetus.[39-39,45] Consequently, the study population was composed of non-pregnant geophagic females. IDA affects the person by decreasing the delivery of oxygen to tissue, in addition causing restless legs syndrome, infertility, cognitive impairment, retarded growth development in children and low-birthweight.[46-52] These factors lead to decreased productivity and quality of life. IDA can also affect the functioning of enzymes that contain iron causing cell abnormalities like hair thinning and diminished cell-mediated immunity.[53]

There is evidence that geophagia and IDA are linked.[7,8,27-30,35,36] The two main reasons for the association rest on two theories depending on the discipline. Geophagia is seen as an adaptive behaviour to obtain minerals that are deficient in the body. However, in the haematology circles geophagia (pica) is seen as a symptom of IDA. Although soil is seen as a means of mineral supplementation, there is contradictory *in vitro* evidence about the availability of iron in soil. Some authors hypothesise that soil might remove dietary iron[11,35,53-56] and others postulating supplementation[33,57-61] of dietary iron. The standard treatment of IDA is with an oral iron preparation to correct the anaemia and replenish the iron stores.[36,39,45] The expected response to oral iron is usually an increase in haemoglobin by roughly 2 g/dl within three weeks.[38] If soil reduces iron bioavailability, then oral iron therapy might not be effective. In addition to the contradictory evidence, the paucity of studies performed on non-pregnant women and studies focusing on the treatment of IDA in geophagia necessitated this study. To unpack this conundrum a study was designed to investigate which theory about soil could be correct, especially when dealing with an *in vivo* human model. The aim of the study was to evaluate the efficacy of oral iron for treatment of iron deficiency anaemia in geophagic females, using red blood cell and iron parameters for evaluation.

Materials and methods

In this randomised single treatment intervention study, 84 non-pregnant geophagic Botshabelo women with mild to moderate IDA were selected to participate in the study. Botshabelo is situated 45 kilometres east of Bloemfontein, the capital city of Free State province, South Africa. This study's proposal was submitted to and approved by the Health Sciences Research Ethics Committee of the University of the Free State, reference number: ETOVS 17/2014. During recruitment, informed consent and family support for participants was sought by giving participants a week to think about their participation and consult with family. From the 320 recruited participants only 84 met the inclusion criteria. The inclusion criteria were as follows: no pregnant or lactating women, haemoglobin <10.5 g/dl, ferritin < 15 µg/L, > 18 years of age, participants should have stayed in Botshabelo for at least six months and consumed soil regularly for a month. The sample size was calculated with OpenEpi version 3, based on an effect of 30% for the haemoglobin results. The average calculated sample size was 77 participants for the three sample size calculation methods.[62]

The participants were randomised into two groups and received oral iron therapy. Group A (n = 45) abstained from soil consumption and group B (n = 39) continued with soil consumption throughout the study period. The rationale for two groups was to indirectly evaluate the effect of soil on iron therapy absorption, that was to observe if stopping consumption of soil would have facilitated iron absorption over the study period. The participants received oral iron therapy over a ten-week period, at a concentration of between 100 and 200 mg elementary iron a day. From baseline and for the first four weeks, all participants consumed one chewable tablet a day equivalent to 100 mg elementary iron. At week four, one capsule was added to the regimen – resulting in a total of 150 mg elementary iron. At week seven, a second capsule was added to the regimen giving a total of 200 mg elementary iron per day. Therapy of IDA is recommended at 100 to 200 mg of elementary iron.[63] Ferrimed® D.S. Chewable Tablets and Ferrimed® Capsules manufactured by Takeda, on behalf of Vifor, were utilised for therapy.[64] The chewable tablet contained 100 mg elementary iron as iron (III)-hydroxide polymaltose complex. Contrary to the chewable tablet, each capsule was composed of 50 mg elementary iron as iron (III)-hydroxide polymaltose complex plus 150 µg folic acid.[64] The total elementary iron dose per participant for ten weeks was 10.15 g. The reason for product selection was because of a palatable taste and the product is stated to have fewer side-effects, thus decreasing the odds of non-compliance or drop-out. Side-effects of oral therapy are dose-dependent, and in addition, adverse events can result in noncompliance of up to 50% of patients.[65] Therefore, the first week was also deemed as a run-in phase to acclimatise participants in taking study medication and to manage the side-effects that may have been encountered secondary to medication.

Two methods were utilised to assess compliance: pill count and questionnaire. For pill count, participants were given a different number of pills and they were required to present the excess number at a subsequent visit for counting. In so doing, an indication of compliance was 'semi'-obtained if the pills added up to the count that was issued at the beginning of the treatment period under review.[66] For the questionnaire method of assessing compliance, data was captured on the side-effects questionnaire.[67] The participants were asked to indicate if they had missed doses and the research team emphasised that missing a dose did not disqualify the participant but would assist the team in understanding anomalous results. Over time a good trust relationship was built with the participants. The data from both methods were combined to obtain an estimated compliance, as both methods allowed, based on their shortcomings. Compliance was calculated for each participant at all visitation periods, namely week 1, 4, 5, 7, and 10.

The procedures and investigations that were undertaken during the study to assess the efficacy of therapy are summarised in Figure 1. The participants were exposed to oral iron therapy while being followed up at different time intervals. In total, six participants were lost to follow-up throughout the study, two from Group A and four from Group B. Blood was drawn at baseline,

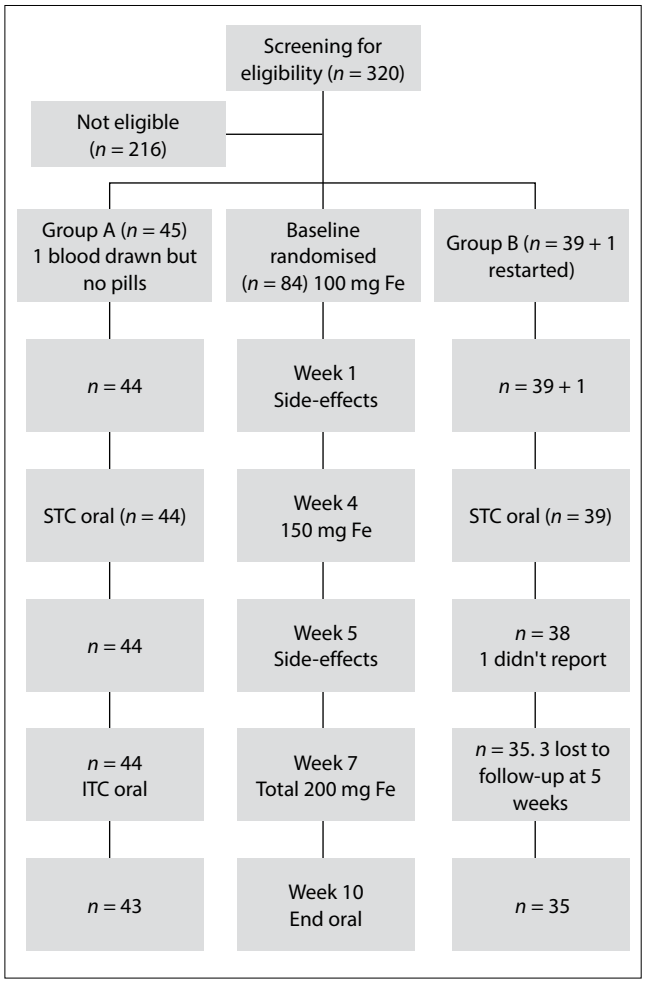

Figure 1: Breakdown of follow-up visit and associated study procedure
ITC – intermediate changes; STC –– short-term changes

week 4 (short-term changes – STC), week 7 (intermediate changes – ITC) and week 10 (end of oral therapy). EDTA and clotted blood specimens were obtained to detect pregnancy, inflammation, assess haematology and clinical chemistry changes associated with IDA correction at each visit; except weeks 1 and 5 which were utilised to assess the side-effects related to the medication. The side-effects questionnaire, that was administered at all study visits, also assessed the geophagia status of every participant. To remain in group A, a threshold of 5% consumption was set and no participant reached this threshold. Furthermore, selected minerals, liver and kidney screening tests were also performed at the beginning and end of the study; the purpose was to assess the general health of the participants (please note that this data is not part of the scope of this article thus it is not presented).

Full blood count was performed at all visits, within four hours of blood collection; using the ABX Pentra 60®.[68] The instrument utilised spectrophotometry; double hydrodynamic sleeving coupled with cytochemistry; current impedance changes and measuring of transmitted light; to measure the different parameters of the full blood count.[68] Iron study analyses were performed using the Siemens Dimension® autoanalyser.[69] The principles of the different tests that were undertaken ranged from immunoturbidimetry, turbimetric, Ferene and Ferene direct.[69]

The statistical analyses were performed utilising the SPSS® program. Data were summarised as means and standard deviation for each measured variable, with a normal distribution. Normality was ascertained by performing the Shapiro-Wilk test and histogram evaluation. In addition, Levene's test for equality of variances was also undertaken to ascertain the *p*-value that should be reported. Paired sample T-test analysis was utilised to compare two study periods of the same group. Independent T-test was employed when comparing different groups. The differences among the data sets within a treatment (baseline, short-term, intermediate-term and end of treatment) group were analysed by repeated-measures analysis of variance (ANOVA). To ascertain sphericity, the Mauchly's test was performed. If the sphericity assumption was not met, then a Greenhouse-Geisser correction was determined. However, data from the variables that produce a non-Gaussian distribution were summarised as median and interquartile range. The difference among follow-up time periods and the different treatment groups were compared utilising the Friedman test and Wilcoxon signed-rank test, respectively. The post-hoc test employed for the Friedman test was the paired Wilcoxon signed-rank test.

Results

The total calculated compliance for the combination of both therapy forms, chewable and capsule [median (IQR)], was 95% (90–99%); 98% (92–100%) and 92% (85–98%) for the entire study population, group A and B, respectively. There was a significant difference (p = 0.031) between group A (median = 98%) and group B (median = 92%), indicating that group A participants were more compliant than group B. Furthermore, the calculated compliance for the different forms of therapy, chewables (p = 0.062) and capsules (p = 0.404) separately, for group A versus B were not significantly different.

Baseline results of the entire study population and study groups post-randomisation

The mean age was 32 years with a range of 18–51 years, with 25% of participants being below 24 years and 25% being above 40 years, as captured in Table I. Mean body mass index (BMI) was just above the reference range; this indicated that approximately half of the participants were overweight (25–29.9 kg/m^2). Less than 16% of participants were considered underweight (< 18.5 kg/m^2) based on the minimum (17.3 kg/m^2) and mean minus standard deviation (19.33 kg/m^2), whereas less than 25% fell in the obese category (> 30 kg/m^2) based on the 75th percentile (29.5 kg/m^2). The BMI data was supported by the waist-hip ratio (WHR) which showed a similar trend. The mean WHR of 0.83 indicated that more than 50% of participants were within the moderate risk category (0.81–0.85). Additionally, greater than 25% were within the high-risk category (> 0.85) based on the 75th percentile of 0.88. The blood pressure measurements of approximately 25% of participants were above the reference range, as witnessed by the 75th percentile of both systolic (142.3 mmHg) and diastolic (89.3 mmHg) measurements. Furthermore, less than 16% of participants had systolic and diastolic blood pressure of more than 156 mmHg and 104 mmHg based on mean plus standard deviation, respectively.

Table I: Baseline anthropometric and general health indicators of the entire study population

VARIABLE	Reference ranges	X ± SD (min-max)	Med [IQR]
Age (years)		32.3 ± 9.3 (18.0–51.0)	36.0 [24.0–40.0]
BMI (kg/m²)	18.5–24.9	25.4 ± 6.1 (17.3–44.3)	24.2 [20.3–29.5]
WHR	≤ 0.80	0.83 ± 0.07 (0.69–1.11)	0.83 [0.76–0.88]
SBP (mmHg)	125 ± 13.6	131.4 ± 24.9 (82.0–205.0)	122.0 [116.0–142.3]
DBP (mmHg)	78 ± 9.9	85.0 ± 18.7 (55.0–144.0)	84.0 [71.8–89.3]

BMI – body mass index; DBP – diastolic blood pressure; IQR – interquartile range; Max – maximum; Med – median; Min – minimum; SBP – systolic blood pressure; SD – standard deviation; WHR – waist:hip ratio; X – mean

At baseline, the participants presented with a hypochromic microcytic anaemia based on the means of mean cell haemoglobin (23.2 pg), mean cell volume (72.9 fl) and haemoglobin (9.2 g/dl) which were below the reference ranges, as expressed in Table II. The serum iron, ferritin and transferrin saturation (TSAT) level of more than 84%, calculated from the mean plus standard deviation (45.1 µg/dL, 14 µg/dL and 10%, respectively), had concentrations below the reference ranges as captured in Table II. Ferritin level signified that those participants with levels below range met the inclusion criteria of the study which was ferritin < 15 µg/L. Group B's mean values were lower than those of group A, potentially signifying a more severe IDA in this group. However, there were no statistically significant changes between the two groups as evidenced by the independent samples t-test *p* values of > 0.05. This finding signified that randomisation was effective and the difference observed was not important.

Mean changes for the entire population throughout the study period

Mean changes of haemoglobin concentration (Hb), mean cell volume (MCV) and mean cell haemoglobin (MCH) indicated an increasing pattern from baseline to the end of oral therapy, as illustrated in Table III. However, this increase was not statistically significant because the repeated measures ANOVA revealed *p* values > 0.05 and clinically insignificant since the mean results did not correct into the reference ranges. In addition, an increase of 2 g/dl in Hb over the ten weeks was observed in only 6.4% (5/78) participants. However, repeated measures ANOVA with Greenhouse-Geisser correction determined that there were statistically significant decreases for total iron binding capacity (TIBC) between different time periods of oral iron therapy $F(2.31, 168.74) = 2.96$, $p = 0.047$. The means of TIBC at all follow-up visits remained above the reference range. Furthermore, there were significant differences for serum iron, ferritin and TSAT between the different oral iron therapy follow-up periods, $\chi2 = 23.132$, $p < 0.001$; $\chi2 = 9.109$, $p = 0.028$ and $\chi2 = 15.580$, $p < 0.001$, respectively. Even though the medians of serum iron, ferritin and TIBC increased from baseline, no parameter improved to such an extent that the values were within the reference values for this population group, as illuminated in Table III.

Mean changes for each study group throughout the study period

Repeated measures ANOVA with Greenhouse-Geisser correction determined that there were statistically significant increases in haemoglobin, MCV and MCH from baseline to week 10; $F(1.42, 62.56) = 4.31$, $p = 0.029$; $F(1.12, 49.23) = 8.19$, $p = 0.005$ and $F(1.23,$

Table II: Baseline results for entire population, group A, B and A vs B (T test *p*-value)

Variable	Reference range[70]	Entire population	Group A mean ± SD	Group B mean ± SD	*p*-value (group A vs B)
Hb (g/dl)	11.5–15.0	9.2 ± 1.5	9.4 ± 1.5	9.0 ± 1.4	0.233
MCV (fl)	81–100	72.9 ± 8.6	73.6 ± 8.6	72.0 ± 8.7	0.395
MCH (g/dl)	27–32	23.2 ± 3.5	23.7 ± 3.4	22.7 ± 3.6	0.198
S Fe (µg/dL)	56–168	26.1 ± 19	28.1 ± 22.3	24.1 ± 14.8	0.409
Ferritin (µg/L)	15–200	8.0 ± 6.0	9.3 ± 7.7	6.7 ± 3.1	0.057
TIBC (µg/L)	250–400	483 ± 77.6	474.4 ± 80	495.3 ± 75.3	0.225
TSAT (%)	16–50	5.6 ± 4.3	6.2 ± 5.4	4.9 ± 2.8	0.211

Ferr – ferritin; Hb – haemoglobin; MCH – mean cell haemoglobin; MCV – mean cell volume; SD – standard deviation; S Fe – serum iron; TIBC – total iron-binding capacity; TSAT – transferrin saturation

Table III: Entire population's results at all follow-up visits

Variable	Baseline mean (IQR)	STC (W4) mean ± SD	ITC (W7)	End (W10)	ANOVA *p*-value
Hb (g/dl)	9.2 ± 1.5*	9.5 ± 1.6	9.6 ± 1.8	9.7 ± 1.8*	0.129
MCV (fl)	72.8 ± 8.9*	72.7 ± 8.7	73.6 ± 9.1	74.4 ± 9.4*	0.307
MCH (g/dl)	23.2 ± 3.6*	23.3 ± 3.7	23.6 ± 3.8	23.9 ± 4.0*	0.323
S Fe (µg/dL)	22 (16–27)*!	22 (17–31)	28.5 (19–41)!	28 (19–40)*	< 0.001
Ferr (µg/L)	6.5 (4–10)*$	7 (4–11)	7 (5–13)*	8 (5–12)$	0.028
TIBC (µg/L)	483 ± 77.6*	497 ± 96.4	436 ± 86.3*	436.5 ± 65.4*	< 0.001
TSAT (%)	4.8 (3.4–6.1)$&	4.9 (3.4–6.9)*!	6.2 (4.4–9.3)&!	6.9 (4.3–9.6)*&	< 0.001

Ferr – ferritin; Hb – haemoglobin; IQR – interquartile range; ITC – intermediate change; MCH – mean cell haemoglobin; MCV – mean cell volume; SD – standard deviation; S Fe – serum iron; STC – short-term changes; TIBC – total iron-binding capacity; TSAT – transferrin saturation; W4, 7, 10 – week 4, 7, 10.
*&$! – means/medians with a similar special character signify statistically significant change between the time periods.

Table IV: Mean changes for group A at different follow up visits

Variable	Baseline mean (IQR)	STC (W4) mean ± SD	ITC (W7)	End (W10)	ANOVA *p*-value
Hb (g/dl)	9.4 ± 1.5*	9.7 ± 1.6	9.9 ± 1.8	10.0 ± 1.7*	0.029
MCV (fl)	73.6 ± 8.6*	74.2 ± 8.4	75.3 ± 8.9	75.7 ± 8.5*	0.005
MCH (g/dl)	23.7 ± 3.4*	24 ± 3.5	24.3 ± 3.5	24.6 ± 3.7*	0.014
S Fe (µg/dL)	22.5 (17–28)*$	24 (18–31)!	29 (21–41)*!	28 (20–40)$	< 0.001
Ferr (µg/L)	7 (4–12.5)	8 (5–16)	8 (5–15)	7 (5–14)	0.038
TIBC (µg/L)	467 (432–516)*&!	441 (411–484)!	430 (404–481)&	441 (389–477)*	0.001
TSAT (%)	4.8 (3.5–6.3)*!	5.1 (3.5–8.1)	6.9 (4.9–10)!	6.9 (4.3–10.7)*	< 0.001

Ferr – ferritin; Hb – haemoglobin; IQR – interquartile range; ITC – intermediate change; MCH – mean cell haemoglobin; MCV – mean cell volume; SD – standard deviation; S Fe – serum iron; STC – short-term changes; TIBC – total iron-binding capacity; TSAT – transferrin saturation; W4, 7, 10 – week 4, 7, 10
*&$! – means/medians with a similar special character signify statistically significant change between the time periods.

49.65) = 6.12, $p = 0.014$, respectively for group A, as depicted in Table IV. Additionally, an increase of 2 g/dl in Hb over the ten weeks was observed in 9.3% (4/43) participants. Furthermore, there were significant differences for serum iron, ferritin, TIBC and TSAT between the different follow-up periods, $\chi2 = 81.707$, $p < 0.001$; $\chi2 = 8.402$, $p = 0.038$; $\chi2 = 15.642$, $p = 0.001$ and $\chi2 = 21.900$, $p < 0.001$, respectively. Post-hoc analysis with Wilcoxon signed-rank tests was conducted for ferritin, the difference between baseline and week 7 did not meet ($p = 0.024$) the Bonferroni correction significance level of $p < 0.008$. The medians for ferritin were below the reference range for all time intervals. The medians of serum iron and TSAT increased from baseline to end of oral iron therapy. For TIBC, the medians dropped from baseline until ITC but increased at the end of oral iron therapy. However, the medians were still outside the reference ranges. Despite all the above-mentioned statistical changes in group A, none were clinically noteworthy.

Haemoglobin concentration of group B revealed a significant change with the overall ANOVA ($p = 0.042$). However, the post-hoc test did not reveal any significant change among the time periods. Furthermore, an increase of 2 g/dl in Hb over the ten weeks was observed in one participant (2.9% = 1/35). The red cell parameters' means were below the reference range, as presented in Table V. Additionally, there were significant differences for serum iron, TIBC and TSAT between the different follow-up periods, $\chi2 = 8.436$, $p = 0.038$; $\chi2 = 14.767$, $p = 0.002$ and $\chi2 = 17.233$, $p < 0.001$, respectively. The medians of serum iron, ferritin and TSAT lingered below the reference range for all oral iron therapy visits as captured in Table V.

Group A showed significant changes with red cell indices and iron study parameters, contrary to group B where the significant changes were only obtained with the iron study parameters. It must be noted that haemoglobin in group B and ferritin for both groups did not show statistically significant changes. Most importantly, the changes in both groups were not clinically significant. One of the objectives of the study was to evaluate if the abstaining group would lead to a better response to oral iron therapy. Thus, factorial ANOVA analysis was undertaken to ascertain if belonging to a group made a difference. A factorial ANOVA with Greenhouse-Geisser correction determined no significant difference for all the parameters, because p values were above 0.05, signifying that belonging to a group did not offer any advantage.

Discussion

From the 320 screened participants only 84 met the inclusion criteria at a rate of 26% that was comparable to the odds ratio of 1.4–2.5 (95% confidence interval) that a geophagic person would have IDA as reported previously.[27] The drop-out rate was 7% (6/84) which was lower than what is expected for a comparable study, e.g. 18%[71] and 22%.[72] The reasons were due to the process followed to obtain consent. Knowing where participants lived also enabled easy follow-up and this approach made participants more comfortable. Reasons for withdrawal of six participants were relocation, losing contact with participants and participants no longer interested in the study.

Compliance was much higher in this study (97%) than other similar studies, e.g. 67%[73] and 50%.[74] High compliance might be explained by the low number of side-effects encountered

Table V: Mean changes for group B at different follow-up visits

Variable	Baseline mean (IQR)	STC (W4) mean ± SD	ITC (W7)	End (W10)	ANOVA *p*-value
Hb (g/dl)	9.0 ± 1.4	9.3 ± 1.5	9.3 ± 1.6	9.3 ± 1.8	0.042
MCV (fl)	72.0 ± 8.7	71.4 ± 8.7	72.1 ± 9.4	72.6 ± 9.8	0.069
MCH (g/dl)	22.7 ± 3.6	22.8 ± 3.8	23.0 ± 4.0	23.1 ± 4.2	0.073
S Fe (µg/dL)	21 (14–27)*!	21.5 (17–39)$	24 (17-41)*$	28 (19–39)!	0.038
Ferr (µg/L)	6 (5–8)	6 (4–8.5)	6 (5-9)	8 (4–10)	0.261
TIBC (µg/L)	493 (439–554)*!	483 (436–546)	434 (399-486)&!	421 (394–496)!	0.002
TSAT (%)	4.3 (3.1–6.1)$&	4.8 (3.3–6.6)*	5.9 (3.9–9.0)&	6.9 (3.9–9.5)*&	0.011

Ferr – ferritin; Hb – haemoglobin; IQR – interquartile range; ITC – intermediate change; MCV – mean cell volume; MCH – mean cell haemoglobin; SD – standard deviation; S Fe – serum iron; STC – short-term changes; TIBC – total iron-binding capacity; TSAT – transferrin saturation; W4, 7, 10 – week 4, 7, 10
*&$! – means/medians with a similar special character signify statistically significant change between the time periods.

due to the type of oral preparation utilised,[75] the individualised follow-up of participants at their own homes and the motivation of participants to quit the habit. There was no preference for either chewables or capsules based on the study group, even though group A had higher compliance rate than group B for the combined therapy form. However, the significant change of A versus B was not clinically noteworthy because the level of compliance for both groups was above the limit that is normally achieved. The age criteria for the study group was within the inclusion criteria and the study's age group was akin to other studies conducted in the Limpopo[76] and KwaZulu Natal[77] provinces, South Africa.

The sample population reflected the general population based on the lifestyle-related findings, namely hypertension and obesity. A quarter of the participants showed a tendency towards hypertension, with almost 16% having stage 2 hypertension (> 160 systolic or >100 diastolic). This is comparable to the 24.4% found in other studies.[78-81] Based on BMI and WHR, more than 50% of participants presented with a common but serious health condition in South Africa namely, obesity. The problem was even worse in 25% of participants as they were classified in the high-risk group. One of the theories of geophagia is its theoretical association with hunger. However, most of the participants were not malnourished but obese. The obesity in this case refutes the hunger theory.

The selection criteria were designed for choosing individuals with mild hypochromic microcytic anaemia and iron study indicators that are associated with IDA. Hence, the entire population data at baseline reflected that. Moreover, there were no significant changes in the full blood count parameters and iron studies indicators, thus the degree of IDA was akin in both groups at baseline. In addition, this finding signified that randomisation produced two similar groups. Therefore, changes observed after treatment were not due to differences between the groups themselves.

Entire study population changes

According to the repeated measures ANOVA there were significant differences for all three IDA related full blood count parameters for the entire study group. These differences were not of clinical importance as the expected response in Hb is an increase of 2 g/dl in 3–4 weeks,[63,82,83] the mean Hb increase was only 0.5 g/dl over a ten-week period. The expected therapeutic response with iron therapy was an increase in serum iron, ferritin and TSAT. All these showed a significant increase especially at ITC and end of oral therapy. However, the response was not of clinical importance. TIBC was expected to decrease during iron therapy, and this was the case. However, TIBC was statistically significant for the same time period. Overall, these results signified that time and increased doses of oral iron did not have a significant impact on therapy outcome. In a case study, similar results were found where a female with geophagia and IDA did not respond to oral iron therapy.[35] It must be noted that, according to the author's knowledge, there were no geophagia-IDA directed therapy studies performed. Therefore, further comparison with other studies was not feasible.

The reasons for the non-responsiveness to oral iron therapy could be due to any of the five below-mentioned hypotheses or a combination of them.[11,35,53-56,84] Kaolinite or soil's constituents could have caused malabsorption of nutritional and treatment iron, thereby interfering with oral iron therapy.[11,35] Alternatively soil directly interfered with iron absorption by coating to the absorptive surface of the gastrointestinal tract thereby interfering with the iron transport across the intestinal wall. [11,54-56] Otherwise, soil due to its abrasive nature could have caused changes to the absorptive surface of the gastrointestinal tract, thus interfering with iron absorption.[11,54-56] On the other hand, soil could have changed the pH of the gastrointestinal tract environment; pH plays an important role in inorganic iron absorption.[11,56] Finally, the theory of daily iron supplementation resulting in increased hepcidin production that would inhibit iron absorption.[53,84] Any of these theories could have been at play either alone or in combination, thus further studies are warranted.

Mean changes for the group that abstained from soil consumption

The red cell parameters Hb, MCV and MCH showed a statistically but not clinically significant increase from baseline to end of oral therapy. TIBC decreased, serum iron and TSAT increased, although overall ANOVA for ferritin was significant, it did not reveal a significant difference in post-hoc analysis. These changes were as expected because they imply that the treatment was minimally successful, but the disappointing fact was that they were not clinically noteworthy. Due to the less than expected improvement on red cell parameters and iron studies, this implied that iron absorption was not optimal, possibly caused by changes to the gastrointestinal tract (GIT) lining.[11,54-56] This leads to the conclusion that oral iron did not correct the red cell parameters of the abstain group sufficiently as the expected therapy outcomes were not encountered. Due to the participant not consuming soil, it can be implied that soil, due to its granular nature, could have caused changes to the GIT absorptive surface thus leading to a suboptimal response to oral iron therapy. However, the non-effectiveness of iron therapy could also be due to another confounding factor.[84] It must be noted that chronic anaemia suppresses hepcidin production,[11] thus daily iron supplementation may still be effective under these conditions. Furthermore, ten weeks might not be enough to revert these GIT changes to normal because of the lack of effective therapy observed in this study.

Mean changes of the group that continued with soil consumption

Hb concentration increased from baseline to STC and then remained the same for the rest of the visits. Serum iron and TSAT increased from baseline to STC, ITC and end of oral therapy, contrary to TIBC which decreased for the same time period. Implying that an increase in therapy iron concentration had a minor impact on iron study results. It must be noted that the changes were not clinically noteworthy indicating that iron

therapy was not effective in this study group. Ferritin did not show significant change as expected because most iron that is absorbed is utilised for red cell synthesis, not diverted to storage. This could imply that soil interfered with iron absorption over and above the changes to the GIT lining postulated in group A. This supposition is supported by group B not showing significant changes in the red cell parameters contrary to group A. Plus fewer participants in group B achieved an increase of 2 g/dl compared to group A.

The significant changes observed signified that some iron was absorbed, although it was not enough to produce a clinically substantial change in the monitored IDA parameters. Therefore, the effects of oral iron therapy were not as expected for treatment of IDA associated with geophagia and abstinence from soil did not show a marked improvement in the IDA parameters. These effects were assessed utilising both red cell and iron study parameters. These effects were observed despite acceptable compliance by participants. More importantly, iron therapy was still not effectively absorbed in the absence of soil in the GIT. This signifies that consumption of soil has a lasting effect of at least ten weeks on the GIT absorption surface resulting in iron malabsorption. Furthermore, data from this study suggest that soil directly interfered with therapy iron absorption and caused malabsorption on the GIT absorptive surface. Therefore, a clinical study investigating the effects of soil on the GIT lining by means of cell culture techniques[56] or gastroscopy is warranted. Another study could also involve assessing the effect of geophagic soils on therapy iron bio-accessibility.[85,86] Furthermore, a multi-centre study involving more participants and alternative day iron supplement is warranted.

Conclusion

In this study oral iron therapy was not effective for the correction of iron deficiency anaemia in geophagic Botshabelo females. These findings imply that the geophagic patient with IDA will carry an unwarranted burden of symptoms for a long time and this may even affect future pregnancy, especially because geophagia affects mostly females of childbearing age and anaemia is associated with low-birth weight. Furthermore, these females will be less productive thus not contributing as effectively to society through their career and have a decreased quality of life. Additionally, the healthcare system will carry the financial burden while ineffective treatment is administered, which places a large burden on an already resource-constrained health system. Therefore it is recommended that further local studies into geophagia-associated IDA are conducted to ascertain the true extent of geophagia nationally, the short- and long-term effects of geophagia on the GIT, the best treatment options for correcting the effects of geophagia on the GIT and how to reverse IDA if geophagia has caused irreversible damage to the GIT.

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Conflict of interest

Author declares no conflict of interest.

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