RESEARCH REPORT

Acute effects of combination of glucosamine sulphate iontophoresis with exercise on fasting plasma glucose of participants with knee osteoarthritis

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KEYWORDS
exercise; fasting plasma glucose; glucosamine sulphate; iontophoresis; osteoarthritis

Abstract
Glucosamine administration is being speculated to alter glucose metabolism and few studies had investigated the effects to confirm this speculation. It is not known if glucosamine sulphate administration through the process of iontophoresis will contradictorily raise the plasma glucose being a sugar. Fifty-two participants with Knee osteoarthritis were randomly assigned to 3 groups: Group 1 participants received exercise therapy followed by administration of 300 mg (an equivalent of 3 mL) of glucosamine sulphate through iontophoresis. Group 2 also received an equivalent of 3 mL glucosamine sulphate iontophoresis without exercise whereas Group 3 received exercise therapy only. Glucometer (One Touch-Ultra easy model) was used to monitor the pre and post fasting plasma glucose. Descriptive and inferential statistics (analysis of variance) were used. The result of analysis of variance showed that there was no significant difference in the final fasting blood sugar (FBS) of the 3 groups. Within session assessment for Group 1 showed that there was also no significant difference in the FBS at different phases of interventions. However, for Group 2, there was significant reduction in FBS immediately after iontophoresis ($p < 0.05$). Similarly, for Group 3, the FBS was significantly lowered immediately after exercise ($p < 0.03$). This study concluded that Glucosamine sulphate iontophoresis did not raise plasma concentration of glucose.

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**Introduction**

In mammals, the blood glucose level is maintained at a reference range between 3.6mM and 5.8mM (mmol/L) and it is regulated by metabolic homeostasis [1]. Exercise is considered a cornerstone in the prevention and correction of excess glucose [2]. Aerobic endurance exercise has been advocated as the most suitable exercise mode to prevent and treat excess glucose [3]. Exercise had been documented to be medicinal [4]. But controversy still trails its effect and efficiency when used in conjunction with other modalities or drugs [5].

There is evidence that osteoarthritis is an inevitable part of aging and it is usually associated with diabetes. Obesity, work-related injuries, and injuries due to sports are also part of the causes of osteoarthritis [6]. The incidence of arthritis is rampant among elite performance athletes compared with nonathletes [7]. Glucosamine (a sugar) is one of the recent nutritional supplements that are being considered as possible means of relieving pain arising from arthritis. Most athletes subscribe to dietary intake of glucosamine supplement to combat inflammation, rehabilitate cartilage, and promote healthier joints [7]. Athletes have discovered the benefits of glucosamine liquid compound in training and daily life [7].

The human body depends on glucosamine, an amino sugar, for the synthesis of connective tissue and cartilage. Glucosamine is used as the starting material for tendons and ligaments, mucous membranes in the digestive and respiratory tracts, and synovial fluid in the joints. It also supports healthy mucus secretion of the digestive, respiratory, and urinary tracts [8]. There is evidence that glucosamine also helps to improve the structure of joints [9]. Braham et al., [10] suggested that glucosamine supplementation could provide some degree of pain relief and improve function in person who experiences regular knee pain, as a result of cartilage injury or osteoarthritis.

The study of the penetration of drugs through the skin has become increasingly important in recent years. The aims of such enhanced and controlled delivery are to maximize the bioavailability of the drug, to optimize the therapeutic efficacy, and to minimize side effects. There are various means of delivering pharmaceutical-drugs medication transcutaneously [11]. The defect usually associated with these methods is side effects in the gastrointestinal tract. To avoid side effects, complementary technique such as iontophoresis is being advocated.

Many topical compositions such as glucosamine sulphate creams have been developed to by-pass the gastrointestinal tract and therefore mitigate the adverse effects associated with oral administration. Such topical compositions also have the additional advantage of acting much faster in relieving pain and inflammation. However, a challenge remains in optimizing and enhancing the therapeutic effects of these topical compositions [12]. Chondroitin sulphate and glucosamine are the best studied and therefore the preferred chondroprotective agents for use in the present invention [12]. A typical dosage of glucosamine salt ranges between 340 mg and 1,500 mg per day, although, a substantial part remains in the liver leaving very little freed glucosamine to reach the cartilage (reduced bioavailability), [13,14]. A dose of 500 mg, an equivalent of 5 mL of glucosamine liquid was observed to be detectable in the plasma [13]. However, Lee et al [14] used what they considered to be a high dose of glucosamine sulphate cream [1000 mg] and they observed a detectable glucosamine within 30 minutes of application. Onigbinde et al [15,16] found that 3 mL of glucosamine sulphate cream, an equivalent of 300 mg, had significant effect in reducing pain among participants with knee osteoarthritis when administered through iontophoresis. Lee et al [14] reported that transdermal delivery of glucosamine is much more effective than oral delivery to the synovial fluid if applied close to the joints.

Only very few studies had investigated the effect of glucosamine on plasma sugar level. Glucosamine is presently in wide use because of its purported beneficial effects in patients with osteoarthritis. Alterations in glucose control have not been documented in trials of short duration exercises conducted in healthy or diabetic participants [17]. It is important to consider glucosamine effect on glucose metabolism, especially when being used in conjunction with exercise therapy. Although exercise depletes glucose, the administration of sugar may increase the glucose concentration.

Theoretically, glucosamine may alter glucose metabolism. Insulin resistance has been noted following intravenous administration of glucosamine in animal studies; however, these findings have not been confirmed in humans. Contradictory reports have continued to trail the effects of glucosamine on blood glucose level [18–20].

Few studies had investigated the effects of glucosamine sulphate on plasma glucose and the modes of administration were through oral or intravenous routes. Furthermore, a few number of participants (14–16 participants) took part in the studies [21,22]. Issues are being raised about the possibility of glucosamine interfering with blood glucose control. A recent review of the literature on this topic concluded that although alterations in glucose metabolism that have been noted in animals gave high glucosamine, similar effects have not been consistently documented in humans following usual oral doses [23].

It appears that there are limited investigations on the effect of glucosamine sulphate iontophoresis on acute exercise-stimulated glucose. Although exercise depletes plasma glucose, it is not known that the glucosamine sulphate administration through iontophoresis will concomitantly raise the plasma glucose, being a sugar. It is suggested that patients with diabetes should monitor their blood glucose levels regularly, if glucosamine is initiated, the dose is increased or the product being taken is changed [23,24].

The primary objective of this study was to determine whether plasma glucose concentration of participants with knee osteoarthritis who received combination of glucosamine sulphate and exercise would differ from that of subjects who received glucosamine sulphate or exercise alone. It was hypothesized that there would be no significant difference in the plasma glucose concentration of participants who received combination of glucosamine sulphate and exercise and those who received glucosamine sulphate or exercise alone.
Methodology

Population of the study

The participants were patients with knee-joint osteoarthritis receiving treatment at the physiotherapy department of Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun State, Nigeria. Sixty participants who met inclusive criteria were recruited from a population of 87 participants with knee osteoarthritis. The sixty participants were randomly assigned into 3 groups with 20 participants in each group, but only 52 participants completed the study. This was as a result of long waiting period for interventions to be completed and those that dropped out could not wait to complete the procedure. All the participants were non-diabetic, non-athletic, and were without nutritional disorders. Furthermore, participants who presented with malnutrition, fever, tumors, cardiovascular disorders, pregnancy, skin diseases, knee osteoarthritis greater than 3 months duration of onset, and those with cardiac pacemaker or any metallic implant were excluded from the study.

Sample and sampling technique

The sample consisted of purposively selected patients with knee-joint osteoarthritis who consented to participate in the study. They were randomly assigned to 3 groups. The random assignment was in order of arrival, that is, the first participant was selected into Group 1, second participant to Group 2, and 3rd participant to Group 3; the 4th to Group 1 again and this continued in that order.

Research design

This study was a quasi-experimental design. Blood samples were obtained before (pretest) and immediately after each intervention (posttest).

Instrumentation

A Bathroom Weighing Scale (Hanson, Germany), modified was used to measure the weights of each participant and it was graded in kilogram whereas a Stadiometer was used to measure the height of each participant. An Electrical Stimulator (Model: Endomed 582, 10060; Enraf Nonius) was used as the source of interrupted galvanic current for the purpose of iontophoresis. The accessories are stimulation tray, which consisted of a bottle containing 70% alcohol to clean the surface of the skin where electrodes was placed; cotton wool; a bowl of water; and lint, which was used to cover the electrodes of the stimulator during iontophoresis. Spatula was used to quantify the amount of Urah Transdermal glucosamine sulphate cream (glucosamine sulphate 8% w/w), 300 mg, an equivalent of 3 mL [5]. Glucometer (One Touch-Utra easy model; LIFESCAN-Johnson & Johnson Company, 021-195) was used to determine the blood sugar level (Fasting plasma glucose in mg/dL). Other accessories are lancet needle, injector, and test strips whereas Cycle ergometer (Bodyguard model) was used as the exerciser.

Before the study, a pilot study was conducted to determine the reliability of the glucometer. Ten participants were recruited for the reliability study. On Day 1, their fasting blood sugar (FBS) was obtained and they were subjected to repeated tests on Day 2 after 1 week. The reliability coefficient was computed and it was found to be 0.93 ($p > 0.05$). This showed that the glucometer is reliable for measuring FBS. Furthermore, the glucometer was found to be highly sensitive and specific and its result correlates significantly well with the laboratory method [25].

Procedure for data collection

Approval was granted by the Ethic and Research Board of Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun State Nigeria. The participants were randomly selected into 3 groups: Group 1 comprises 20 participants who received exercise therapy followed by glucosamine sulphate iontophoresis. Group 2 comprises 15 participants who received glucosamine sulphate iontophoresis without exercise whereas Group 3 comprises 17 participants who received exercise therapy alone.

The first group exercised on cycle ergometer for 15 minutes after which they received 300 mg of glucosamine sulphate cream (an equivalent of 3 mL) by means of Electrical Stimulator. Glucosamine cream was placed on the active electrodes (glucosamine being the active ingredient is positively charged), [26]. The active electrode was placed on the medial side of the knee (after the skin surface was cleaned with 70% alcohol to minimize the risk of burns [27]). The inactive electrode was placed on the lateral side of the knee joint. With both electrodes held in place by an adhesive strap, the stimulator was switched on, turned to direct current mode, and the intensity was gradually increased and maintained at the patient’s pain threshold for 15 minutes [28]. For Group 1, a drop of blood sample was obtained through the use of a sterile lancet tip on the thumb of each participant before ergometer exercise (pretest), immediately after exercise, immediately after iontophoresis (post test), and 30 minutes post iontophoresis [21,29]. The recovery glucose was monitored at 30 minutes post iontophoresis. Most participants had detectable glucosamine at 30–45 minutes, even as early as 15 minutes [18].

The second group received the same quantity of glucosamine sulphate cream and the same process of iontophoresis as in Group 1 but without any form of exercise. The 3rd group, which served as control, received only cycle ergometry for 15 minute. The FBS value was obtained for the participants as in Group 1 using Glucometer . All the subjects fasted overnight (with last meal not exceeding 10 pm of the previous day) and all morning drugs were withheld on measurement days until after the experimental procedure. At each testing, fresh needle was used for each of the participant at every prick to avoid cross infection.

Data analysis

Both the descriptive and inferential statistics were used. The descriptive statistic was used to describe the data obtained.
It was used to determine the mean and standard deviation for age, body mass index, weight, and plasma glucose level. An inferential statistic- analysis of variance was used to determine the significant differences in blood sugar levels of the 3 groups. Post hoc analyses were done to show the mean differences of the variables where significant differences were observed. The level of significance was set as 0.05.

Results

The result of the anthropometric parameters was presented in Table 1. The result showed 3.5% drop in FBS immediately after exercise and a further drop by 2.05% after glucosamine sulphate iontophoresis whereas the recovery of FBS after 30 minutes of resting increased by 0.25%. The total decrease in FBS was 5.20% between initial FBS and final FBS (after 30 minutes resting), (Table 2).

Similarly, for Group 2 participants, the FBS after iontophoresis dropped by 10.85% whereas the FBS further dropped by 3.48% after 30 minutes resting. The total drop in FBS from initial value to final FBS after 30 minutes was 13.95% (Table 3). For Group 3 participants there was 6.58% decrease in FBS. The recovery FBS after 30 minutes further dropped by 2.19% showing a total drop in FBS from initial value to final FBS after 30 minutes by 8.62% (Table 3).

The result of the analysis of variance showed that there was no significant difference in the initial FBS of the 3 groups (F = 0.526, p > 0.05). Similarly, there was no significant difference in the final FBS of the 3 groups (F = 1.27, p > 0.29). Furthermore, there was no significant difference in the recovery of final blood sugar of the 3 groups after 30 minutes rest (F = 2.82, p > 0.05), (Table 2).

Comparison of FBS within the groups

There was also no significant difference in the FBS of Group 1 participants when the initial FBS was compared with the FBS immediately after exercise on cycle ergometer, immediately after glucosamine sulphate iontophoresis, and immediately after 30 minutes of rest (F = 1.21, p > 0.31). However, there was significant difference in the FBS of Group 2 participants who had only glucosamine sulphate iontophoresis when the initial FBS was compared with the FBS immediately after iontophoresis and immediately after 30 minutes of rest (F = 8.90, p < 0.001). The result of the Post hoc analysis (Scheffe) showed that there was significant reduction in FBS after iontophoresis, (p < 0.05) and after 30 minutes of rest (p < 0.001), (Table 3).

Similarly, among Group 3 participants who exercised on cycle ergometer alone, there was significant difference (F = 6.78, p < 0.03) when the initial FBS was compared with the FBS immediately after exercise and after 30 minutes rest. The result of the Post hoc analysis showed that the FBS was significantly lower immediately after exercise (p < 0.03) and after 30 minutes rest (p < 0.004), (Table 4).

Discussion

Drug education, actions, and interactions are areas where attention should be focused, especially in areas where

\[ \text{Table 2: Result of comparison of FBS across the 3 groups} \]

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Mean FBS</th>
<th>SD</th>
<th>F</th>
<th>p</th>
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<tbody>
<tr>
<td>Initial</td>
<td>1</td>
<td>126.10</td>
<td>13.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>129.00</td>
<td>9.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>129.65</td>
<td>9.91</td>
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<td>0.59</td>
</tr>
<tr>
<td>Final</td>
<td>1</td>
<td>119.20</td>
<td>12.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>115.00</td>
<td>10.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>121.12</td>
<td>9.26</td>
<td>1.27</td>
<td>0.29</td>
</tr>
<tr>
<td>FBS 30 min</td>
<td>1</td>
<td>119.50</td>
<td>12.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>111.00</td>
<td>11.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>118.47</td>
<td>8.52</td>
<td>2.82</td>
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</tr>
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</table>

FBS = fasting blood sugar; SD = standard deviation.

\[ \text{Table 3: Comparison of the FBS within each group} \]

<table>
<thead>
<tr>
<th></th>
<th>Mean FBS</th>
<th>SD</th>
<th>% decrease</th>
<th>F</th>
<th>p</th>
</tr>
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<td><strong>Group 1</strong></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Initial</td>
<td>126.10</td>
<td>13.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After exercise</td>
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<td>13.68</td>
<td>3.50</td>
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<td></td>
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<tr>
<td>After iontophoresis</td>
<td>119.20</td>
<td>12.94</td>
<td>2.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 30 min</td>
<td>119.50</td>
<td>12.67</td>
<td>0.25*</td>
<td>1.21</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>129.58</td>
<td>9.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After iontophoresis</td>
<td>115.00</td>
<td>10.10</td>
<td>9.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 30 min</td>
<td>111.00</td>
<td>11.64</td>
<td>0.25*</td>
<td>8.90</td>
<td>0.001**</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>129.65</td>
<td>9.91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After exercise</td>
<td>121.18</td>
<td>9.26</td>
<td>8.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 30 min</td>
<td>118.47</td>
<td>8.52</td>
<td>2.19</td>
<td>6.78</td>
<td>0.03*</td>
</tr>
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</table>

*Significant at p < 0.05; **Significant at p < 0.001.

FBS = fasting blood sugar; SD = standard deviation.
there are overlaps in action of drugs and exercise therapy such as in glucose control. Medical evaluation is a premier step in exercise training prescription [30]. There are a variety of conditions that need to be considered in understanding hypoglycemia during exercise, including the type and duration of exercise and glucose concentrations before starting exercise. Human blood glucose levels normally remain within a remarkably narrow range. In most humans this varies from 80 mg/dL to 110 mg/dL (4 mmol/L to 6 mmol/L) except shortly after eating, when the blood glucose level rises temporarily up to may be 140 mg/dL (7–8 mmol/L) or a bit more in nondiabetics [31]. The homeostatic mechanism, which regulates the blood value of glucose in a remarkably narrow range, comprises several interacting systems, of which hormone regulation is the most important. Glucosamine has been observed to cause insulin resistance by inhibiting insulin-stimulated glucose transport in the hexosamine pathway [32].

This study used a single dose because Biggee et al [18] used a single dose of glucosamine as it disappears from human plasma by 5 hours and also because of a study with dogs that found no significant differences between single dose and multiple dose pharmacokinetics [33]. The result of this study showed that there was no significant difference in the final FBS of the participants who had combination of both exercise therapy and iontophoresis, those who had only glucosamine sulphate iontophoresis, and those who had exercise therapy alone. This study tended to support that of Stumpf and Lin [27] who also reported that glucosamine did not affect glucose tolerance or insulin resistance in nondiabetic subjects. Similarly, Joseph et al [22] observed that despite long duration treatment with glucosamine sulphate for 4 weeks, there was no change in fasting plasma glucose. Stumpf and Lin [17] also reported that small and short-term studies suggested that glucosamine may be used in selected patients without affecting glucose control. This present finding still lent support to that of Biggee et al [18] who also found an insignificant mean incremental elevation in plasma glucose among osteoarthritic subjects, although, they suggested that glucosamine ingestion may affect glucose levels and consequent glucose uptake in patients who have untreated diabetes or glucose intolerance.

Iontophoresis has been demonstrated to “drive” some drugs to a tissue depth of 5–20 mm even up to 1.7 cm [34]. Despite the amount of glucosamine in blood after oral administration, it was only a quarter of the amount that is available after intravenous and intramuscular administrations [35]. The actual concentration of glucose in blood is very low, even in the hyperglycemic [1]. Although iontophoresis delivers less than a local injection, it provides much higher local concentrations than oral administration [36]. Transdermal administration means that the drug may be introduced into the systemic circulation without initially entering the portal circulation where it may be metabolized into a pharmacologically inactive form (first pass effect) [37]. During iontophoresis, drug is delivered directly into the bloodstream without delays due to absorption through the gastrointestinal tract.

There were also no significant changes in the FBS within Group 1 participants at different phases of intervention, when the initial FBS was compared with the FBS immediately after exercise on cycle ergometer and immediately after glucosamine sulphate iontophoresis. However, there was significant reduction in the FBS of Group 2 participants immediately after glucosamine sulphate iontophoresis and after 30 minutes of rest with significant reduction of 10.85% and 3.48%, respectively in the plasma glucose. This may be attributed to a process of reverse iontophoresis. In reverse iontophoresis the negative charge of the skin at buffered pH causes it to be permselective to cations causing solvent flow towards the anode. This flow is the dominant force allowing movement of neutral molecules, including glucose, across the skin [38]. The reduction in glucose level was almost comparable with that observed using exercise to deplete glucose [24].

Among Group 3 participants, the FBS was significantly lowered immediately after exercise and after 30 minutes rest with 8.62% and 2.19% reduction respectively. The reduction found in this study was low when compared with that of previous studies. This may be attributed to knee joint impairment that arose from the pathological effects of knee osteoarthritis. The participants were unable to pedal with high intensity on the ergometer. Zinman [39] reported that in diabetic subjects, an acute glucose-lowering effect occurred with each exercise session. Gale [20] reported that immediately after low-intensity exercise the incremental glucose was reduced by 16%. They also observed that after the high-intensity exercise, the incremental glucose area reduced by 14% immediately after exercise and 35% 24 hours after exercise.

Most drugs that are otherwise suitable for transdermal delivery do not achieve sufficiently high blood levels for pharmacological activity when administered transdermally, hence, it is sometimes necessary to enhance this delivery. This can be achieved by chemical means namely by the use of absorption promoters such as dimethylsulfoxide, Azone (Trade Mark), and surfactants [40,41].

The limitations of this study were lack of true randomization and the inability to ascertain if the quantity of

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2 initial FBS</td>
<td>FBS after iontophoresis</td>
<td>8.40</td>
</tr>
<tr>
<td></td>
<td>FBS after 30 min</td>
<td>18.00</td>
</tr>
<tr>
<td>Group 3 initial FBS</td>
<td>FBS after exercise</td>
<td>8.53</td>
</tr>
<tr>
<td></td>
<td>FBS after 30 min</td>
<td>11.18</td>
</tr>
</tbody>
</table>

*Significant at p < 0.001; **Significant at p < 0.05; ***Significant at p < 0.01.

FBS = fasting blood sugar.
Glucosamine administered in this study was adequate enough to affect the plasma glucose concentration. This study concluded that glucosamine sulphate did not have significant effect on plasma glucose of participants with knee osteoarthritis.

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References


