Original Article

Altered olfaction, obesity, and glycosylated hemoglobin; Indicators of accelerated ageing in apparently healthy, Pakistan's young aged population.

Faizan Mirza1,2, Amaila Fazal3, Najia Siddiqui1,2 & Sadaf Ahmed1,2,4

1Department of Physiology, University of Karachi, Karachi-Pakistan
2Psychophysiology Research Lab, MAHQ Biological Research Centre, University of Karachi, Karachi-Pakistan
3Epidemiology and Public Health, Dadabhoy Institute of Higher Education, Karachi-Pakistan
4Advanced Educational Institute & Research Centre, Karachi-Pakistan

Abstract

Background: Obesity is an associated risk of devastating diseases and increased mortality. Thereby, the study objective was to evaluate the predisposing obese individuals towards accelerated ageing and determine the smell test as the possible indicator for early biological ageing.

Methodology: This was a descriptive cross-sectional study carried out in Karachi, Pakistan, from 8th June 2016- 4th December 2019. A total of 412 individuals were included in the study. The data for age, gender, body mass index (BMI), sniffing score, and hemoglobin A1c (HbA1c) levels were collected from the target population. The screening 12 test was intended to be used for the examination of smell disorders in humans. The test results were used to differentiate between Normosmia, Hyposmia, and Anosmia.

Results: Four hundred and twelve participants were recruited in the study with a mean age of 32.65±12.6 years and divided into three age groups; 20 to 36, 37 to 53, and 54 to 70 years. There were 194 (47.1 %) females and 218 (52.9 %) males. Out of the total, 19.9 % of individuals were underweight, 58.5 % were normal, 21.6 % were overweight. It was also observed that of the total, 24 % of participants were pre-diabetic. Cross analysis of the variables showed that the olfaction decreased as the BMI was increasing (p=0.000 for obese).

Conclusion: As the sense of olfaction decreased with an increase in BMI and HbA1c levels, it was concluded that obese individuals have an increased predisposition towards accelerated ageing and the increased risk of predisposition to diabetes to obesity significantly accelerate the process of biological ageing.

Keywords

Ageing, Diabetes, Glycosylated Hemoglobin Levels, Obesity, Sniffing Score.
**Introduction**

Obesity is an avoidable medical ailment characterized by enlarged fat deposition inside the body due to augmented caloric intake and lesser physical activity. It is an associated risk of devastating diseases and increased mortality. Globally, World Health Organization (WHO) uses BMI to classify overweight and obese individuals, excluding Asians because of a much lower BMI cut-off as they have an increased risk of morbidity following obesity. In February 2000, Body Mass Index cut-offs for Asian Pacific overweight adults were reported by the WHO as >23 while >25 for being obese.

The prevalence of obesity increased rapidly in developing and developed nations indicating that the tendency is mostly due to environmental, behavioral, and social changes, even though hereditary factors could be involved. Historically, obesity was associated with socioeconomic status (SES); however, an inverse relation had been observed between the obesity prevalence and the affluence over the last five decades, predominantly in women as compared to men.

Developing countries are going under the epidemiologic and demographic transitions progressively, including a nutritional shift characterized by the consumption of more refined sugar and fats despite grains, pulses, and carbohydrates, and the higher quantities of red meat. A Healthy obese individual does not have any 'associated' diabetes, hypertension, and even atherosclerosis risk. However, previous studies had shown that obesity proves to be an independent risk of cardiovascular diseases.

Although obesity has appeared as an epidemic worldwide, it is still under-recognized in Pakistan. Pakistan is currently undergoing an obesity epidemic. In Pakistan, the causative factors of obesity are urbanization, environmental changes, highly dense food consumption, lifestyle modification, and physical inactivity.

Adiposity is measured through BMI; however, it should be realized critically that all sites in the body are not equal in adiposity. Intra-abdominal (central) fat deposits compared to peripheral fat deposits are generally more strongly linked to Diabetes mellitus and insulin resistance. Studies have demonstrated that abdominal obesity is imperative to biological ageing due to insulin resistance and glucose intolerance. Data from the literature demonstrate that olfactory deficits are commonly found both in ageing. Age-related atrophy is seen with ageing in nasal epithelium. An increase in nasal volume as a function of age lowers the blood flow in the region as well as reduced responsiveness to autonomic stimulation. Thereby, the study objective was to evaluate the predisposition of young obese individuals towards accelerated biological ageing and to determine that a smell test is a possible indicator for accelerated biological ageing.

**Methodology**

This descriptive cross-sectional study was carried out in Karachi, Pakistan, from 8th June 2016-4th December 2019. A total of 412 community-dwelling, apparently healthy individuals with no diagnosed illness and disorder, were included in the study. The data for age, gender, SES, longevity in family, education status, marital status, BMI, sniffing score, and HbA1c levels were collected from the target population. This study was approved by the institution’s ethics and review board committee (Reference Number: QR/957/NMC/10). The informed consent was taken from all the participants before the start of the study.

The operational definition of healthy ageing (a focus of WHO 2015-2030) was used in the study rather than just ageing. WHO defines Healthy Ageing “as the process of developing and maintaining the functional ability that enables wellbeing in older age.”

For BMI calculation, subjects were asked to take off shoes, and body mass was noted using physical balance, and height was measured, making them stand against the measuring tape. Thus, BMI was calculated by the formula: BMI = kg/m². Where a person’s weight was in kilograms and height was in
meters square. WHO guideline cut-offs were used. A BMI of 30.0 or more was considered obese whereas, 25.0 to 29.9 was overweight, while the healthy range was 18.5 to 24.9.

HbA1c test was performed by HB hemoglobin auto analyzer High-Performance Liquid Chromatography (HPLC method) (Lifotronic H8 hemoglobin analyzer). 4 ml blood was collected by venipuncture using a vacutainer, in KEDTA tube (Lavender top). The lysis of cells was performed, and samples were incubated at 37 ºC to eliminate unstable aldime formation. The supernatant was collected after centrifugation and injected into the HPLC system. The gradient separation was done via HPLC at 30ºC. The last 5 minute’s chromatogram was recorded using a UV detector. The blood calibrator was used for quantification, and the peak height integration was used to calculate concentration.

Furthermore, for smell identification, screening 12 test kit of Sniffin Sticks (Burghart, MESSTECHNIK) intended to be used for examination of smell disorders in human subjects was used. The test results were used to differentiate between Normosmia, Hyposmia, and Anosmia. Sniffing scores (odors correctly identified) from The Sniffin’ Sticks test manual was used, normosmia 10-12, hyposmia 6-10, anosmia 0-6 (Burghardt®, Wedel, Germany). Before the beginning of the test, each patient was asked for any known odor allergies. The Sniffing sticks screening 12 test method was based on the forced-choice method; as per the instructions manual, the subject had to answer after each Sniffing stick according to the presented choice card, even if they did not detect anything. This procedure does not lead to a corruption of the score because only a statistic random value of guessing can be achieved.

The test consists of felt pens, the tips of which are impregnated with 4 ml of odorant fluid or odorant substance dissolved in propylene glycol and an antibacterial agent. The provided kit had 12 scent pens, a holder, 12 multiple choice cards, a multilingual manual, an answer block with an answer template, an evaluation block. It was made sure that the subject had not consumed any food, drinks, or cigarettes 15 minutes before testing. The only exception was drinking water. Odor-free gloves were used during the test for presenting each test pen. Fresh pair of gloves for each individual was used. Care was taken to make sure scent pens end did not come in contact with gloves.

Before presenting the Sniffing Stick, subjects were handed out the corresponding choice card (a total of 12 cards 1-12, each corresponding to the respectively labeled pen). A respective scent pen was uncapped, and the subject was asked to inhale. A defined phrase: “Please Sniff Now” to instruct the individual to inhale was used as standard protocol mentioned by the manufacturer. The tip was held 2 cm below the nose medially to both nostrils, while the subject inhaled for 3-4 seconds. The individuals were asked to choose a term on the choice card (4 options printed, A-D with 3 incorrect and 1 correct option) mark the answer on the identification sheet. The procedure was repeated for each pen with a minimum pause of 30 seconds, and all answers were marked on the identification sheet.

The experiment was conducted in a well-ventilated room to avoid residual odor; the examiner washed hands with running water and wore cotton gloves. It was ensured that subjects did not eat, drink or smoke for the past 15 minutes before taking the test. Between each subtest, a gap of 3 minutes was assured, 18 no odor neutralizers used.

The answers were checked and graded using gender-based cum age-matched nomogram provided by the manufacturer. All the data was recorded in an excel sheet that was pre-designed and validated. Categorical data were presented as frequencies and percentages. All statistical calculations were done through SPSS version 18.0. Descriptive statistics were done for categorical variables, while inferential statistics were done through Pearson correlation and cross tabs. One-way ANOVA was used to determine the age-wise alterations in the HbA1c (%) level and smell identification ability. A p-value < 0.05 was
Results

Four hundred and twelve participants were recruited in the study with a mean age of 32.65±12.6 years. Participants were divided into three age groups 20 to 36, 37 to 53, and 54 to 70 years. The study was conducted on both genders consisting of 194 females and 218 males. Out of the total, 19.9 % of individuals were underweight, 58.5 % were normal, 21.6 % were overweight. It was also observed that of the total, 24 % of participants were pre-diabetic due to altered HbA1c levels. When the Smell Identification Test was performed, 78.6 % of individuals were found to be having hyposmia, normosomia was in 20.4 %, and 1.0 % had anosmia (Table 1).

| Demographic Variables | Sub-Categories | Mean±SD |
|-----------------------|----------------|---------|
| Age (Years)           |                | 32.65±12.624 |
| BMI (kg/m²)           |                | 22.696±5.7073 |
| W/H Ratio             |                | 0.8107±0.23115 |
| HbA1c (%)             |                | 5.3443±0.45058 |
| Sniffing Score        |                | 9.00±1.654 |
| n(%)                  | Male           | 218(52.9) |
|                       | Female         | 194(47.1) |
| Marital Status        | Single         | 231(56.1) |
|                       | Married        | 181(43.9) |
| Age Groups (Years)    | 20 to 36       | 292(70.9) |
|                       | 37 to 53       | 68(16.5) |
|                       | 54 to 70       | 52(12.6) |
| Obesity               | Underweight    | 82(19.9) |
|                       | Normal         | 241(58.5) |
|                       | Overweight     | 89(21.6) |
| Socioeconomic Status  | Low SES        | 143(34.7) |
|                       | Middle SES     | 103(25.0) |
|                       | Upper Middle SES | 157(38.1) |
|                       | Upper SES      | 9(2.2) |
| Education             | Post-graduate  | 91(22.1) |
|                       | Graduate       | 113(27.4) |
|                       | Undergraduate  | 4(1.0) |
|                       | Intermediate   | 32(7.8) |
|                       | Matric         | 40(9.7) |
|                       | Secondary      | 9(2.2) |
|                       | Primary        | 8(1.9) |
|                       | Illiterate     | 115(27.9) |
| Smell Identification Ability | Anosmia | 4(1.0) |
|                       | Hyposmia       | 324(78.6) |
|                       | Normosomia     | 84(20.4) |
| Diabetes Status       | Normal         | 301(73.1) |
|                       | Pre-diabetic   | 99(24.0) |
|                       | Diabetic       | 12(2.9) |

*HbA1c-hemoglobin A1c; BMI-Body Mass Index; W/H Ratio-Waist to Hip Ratio
Out of the total, 301 subjects were normal, 99 were pre-diabetic, and 12 were diabetic. SES, education, marital status, BMI and age significantly affected the HbA1c level among the studied population (p<0.05). Table 2 shows the association of HbA1c with our study characteristics.

| Variable            | HbA1c n(%)                  | p-value |
|---------------------|-----------------------------|---------|
|                     | Normal (n=301) | Pre-diabetes (n=99) | Diabetes (n=12) |
| Gender              |               |                   |                  |
| Male                | 169(56.1)     | 45(45.5)          | 4(33.3)          | 0.070 |
| Female              | 132(43.9)     | 54(54.5)          | 8(66.7)          |
| SES                 |               |                   |                  |
| Middle SES          | 73(24.3)      | 30(30.3)          |                  | 0.000* |
| Upper middle SES    | 108(35.9)     | 37(37.4)          | 12(100)          |
| Low SES             | 111(36.9)     | 32(32.3)          |                  |
| Upper SES           | 9(3.0)        |                   |                  |
| Education           |               |                   |                  |
| Post-graduate       | 66(21.9)      | 21(21.2)          | 4(33.3)          | 0.000* |
| Graduate            | 81(26.9)      | 32(32.3)          |                  |
| Undergraduate       | 4(1.3)        |                   |                  |
| Intermediate        | 24(8.0)       | 4(4.0)            | 4(33.3)          |
| Matric              | 24(8.0)       | 12(12.1)          | 4(33.3)          |
| Secondary           | 4(1.3)        | 5(5.1)            |                  |
| Primary             | 8(2.7)        |                   |                  |
| Illiterate          | 90(29.9)      | 25(25.3)          |                  |
| Marital status      |               |                   |                  |
| Single              | 195(64.8)     | 36(36.4)          |                  | 0.000* |
| Married             | 106(35.2)     | 63(63.6)          | 12(100)          |
| Obesity             |               |                   |                  |
| Underweight         | 74(24.6)      | 8(8.1)            |                  | 0.003* |
| Normal              | 168(55.8)     | 65(65.7)          | 8(66.7)          |
| Overweight          | 59(19.6)      | 26(26.3)          | 4(33.3)          |
| Age Group           |               |                   |                  |
| 20 to 36            | 244(81.1)     | 48(48.5)          |                  | 0.000* |
| 37 to 53            | 49(16.3)      | 19(19.2)          |                  |
| 54 to 70            | 8(2.7)        | 32(32.3)          | 12(100)          |
| Longevity           |               |                   |                  |
| Present             | 235(78.1)     | 71(71.7)          | 8(66.7)          | 0.320 |
| Absent              | 66(21.9)      | 28(28.3)          | 4(33.3)          |

*Statistically significant; SES-Socioeconomic Status; *HbA1c-hemoglobin A1c
The HbA1c level also significantly increased (median; 25th–75th percentiles) from 5.20; 5.00-5.50 % among 20 to 36 years age group to 6.02; 5.80-6.10 % among 54 to 70 years subjects (Figure 1). The sniff score (smell identification ability) decreased from 9.0; 8.0-11.0 among 20 to 36 years age group to 7.0; 7.0-9.0 among 54 to 70 years age group (Figure 2).
The majority of the enrolled study participants were hyposmic (n=324), the smell identification ability was significantly associated with socioeconomic status, education, marital status, obesity, age and longevity (p<0.05) (Table 3).

Table 3: Association of Smell Identification Ability (Sniff Score) with study characteristics

| Variable     | Smell Identification-Sniff Score n(%) | p-value |
|--------------|--------------------------------------|---------|
|              | Anosmia (n=4) | Hyposmia (n=324) | Normosmia (n=84) |
| Gender       | Male 4(100)     | 174(53.7)      | 40(47.6)      | 0.101 |
|              | Female -        | 150(46.3)      | 44(52.4)      |
| SES          | Middle SES -    | 83(25.6)       | 20(23.8)      | 0.031* |
|              | Upper middle SES 4(100) | 129(39.8) | 24(28.6)      |
|              | Low SES -       | 107(33.0)      | 36(42.9)      |
|              | Upper SES -     | 5(1.5)         | 4(4.8)        |
| Education    | Post-graduate - | 79(24.4)       | 12(14.3)      | 0.000* |
|              | Graduate -      | 81(25.0)       | 32(38.1)      |
|              | Undergraduate - | -               | 4(4.8)        |
|              | Intermediate 4(100) | 24(7.4)     | 4(4.8)        |
|              | Matric -        | 24(7.4)        | 16(19.0)      |
|              | Secondary -     | 9(2.8)         | -             |
|              | Primary -       | 8(2.5)         | -             |
|              | Illiterate -    | 99(30.6)       | 16(19.0)      |
| Marital status | Single -       | 179(55.2)      | 52(61.9)      | 0.042* |
|              | Married 4(100) | 145(44.8)      | 32(38.1)      |
| Obesity      | Underweight -   | 62(19.1)       | 20(23.8)      | 0.000* |
|              | Normal 4(100)   | 205(63.3)      | 32(38.1)      |
|              | Overweight -    | 57(17.6)       | 32(38.1)      |
| Age Group    | 20 to 36 4(100) | 212(65.4)      | 76(90.5)      | 0.000* |
|              | 37 to 53 -     | 68(21.0)       | -             |
|              | 54 to 70 -     | 44(13.6)       | 8(9.5)        |
| Longevity    | Present 4(100) | 254(78.4)      | 56(66.7)      | 0.042* |
|              | Absent -        | 70(21.6)       | 28(33.3)      |

*Statistically significant

Discussion

Obesity is an associated risk of debilitating diseases and increased mortality. In Pakistan, the causative factors of obesity are urbanization, environmental changes, highly dense food consumption, lifestyle modification, and physical inactivity. Adiposity is measured through BMI; however, it should be realized critically that all sites in the body are not equal in adiposity. The intra-abdominal (central) fat deposits as compared to peripheral fat deposits are more strongly linked to Diabetes mellitus and insulin resistance. Therefore, it was hypothesized that obese individuals are inclined towards an accelerated ageing process. A total of 412 individuals were recruited in the study and divided into three age groups: 20 to 36, 37 to 53, and 54 to 70 years. The genders were included in the study 194 (47.1 %) females and 218 (52.9 %) males. Out of the total, 89 (21.6 %) were obese, and 99 (24 %) were pre-diabetic.

When the association between body physique (BMI) and predisposition to diabetes (HbA1c) was
observed, it was found that the HbA1c level becomes altered with obesity and the risk of predisposition to diabetes increases with increased BMI significantly \( (p=0.003) \). This is because enlarged fat cell releases leptin in large quantities. Followed by Leptin deficiency that ultimately leads to obesity\(^{19,20}\). The fat cell’s increased size is mainly attributed to the amplified free fatty acids’ concentration, thereby producing modifications in the cholesterol metabolism and insulin clearance by the liver, ultimately leading to the increased gall bladder disease and diabetes risk following obesity\(^{21}\). Therefore, researchers have considered obesity as the strongest predictor of type II diabetes mellitus\(^{22}\). And thus its development typically depends on changes in one or both insulin sensitivity and insulin secretion, which could be modified by obesity\(^{23}\).

Besides, when the association between body physique (BMI) and olfaction (smell identification test) was observed, it was found that the risk of decreased smell identification ability was almost equally prevalent in underweight, normal, and overweight individuals. Hence, a statistically significant association \( (p=0.000) \) showing an increased risk of hyposmia and anosmia with increased BMI was concluded. These results were in agreement with the previous studies. Researches have demonstrated that abdominal obesity is imperative to biological ageing due to insulin resistance and glucose intolerance\(^{12}\). Whereas, disorders of olfaction are generally associated with advancing age, especially affecting the elderly people who have cognitive impairment\(^{24}\). Thereby, it was confirmed through the results that decreased sense of olfaction at younger ages is untimely predisposing obese individuals towards accelerated ageing.

However, when the cross-analysis was done between the age groups, their BMI status, and smell identification test, it was observed that olfaction was decreasing in all age groups irrespective of BMI. Statistically non-significant association \( (p=0.765) \) was found between the two variables. Recent research confirmed these results, which showed that obesity or increased BMI causes malfunctioning of the hypothalamus. This is ultimately leading to an imbalance between the intake of calories and energy expenditure, which results in a decreased life span due to a positive balance of energy\(^{25}\).

Additionally, when the cross-analysis was done between the age groups, their predisposition to diabetes and smell identification test, it was observed that olfaction was decreasing in all age groups as the HbA1c levels were increasing. Statistically non-significant association \( (p=0.106) \) but showing altered olfaction in age groups, specifically in the age group of 37-53 years as the risk of diabetes increases due to altered HbA1c levels, thereby proving accelerated ageing in the diabetic and pre-diabetic young individuals considering altered olfaction as a possible indicator of ageing. The current results were similar to previous research, which revealed that olfaction test gave non-significant results between the patients with and without complications of diabetes\(^{26}\). A decline in cognitive functions are a hallmark of diabetes that leads to late-onset dementia\(^{27}\). The Mona Lisa Study highlighted that obesity and increased blood glucose is directly linked with poor cognitive impairment and is already evident in middle-aged individuals\(^{28}\).

Studies have suggested that olfaction disorders are basically due to neuro-degeneration and could occur as a diabetic complication\(^{29}\). Since impaired olfaction is an indicator of ageing in the elderly, but it was observed in the early ages in the current study due the presence of diabetes and obesity in the study participants. These results confirms the findings of the previous research where obesity and diabetes were predisposing individuals towards accelerated ageing\(^{30}\).

As olfaction is subsiding with an increase in BMI and HbA1c levels, it was concluded that obese individuals are going towards accelerated biological ageing and their predisposition towards diabetes due to obesity is increasing. The study’s novelty lies in the finding that the smell identification test was accepted as a physiological indicator of ageing. In the wake of such findings, exercise is highly recommended if Pakistan wants
to reduce the non-communicable diseases’ burden within the next two decades. Otherwise, the long-term effects would be anything but beneficial in children and adults.\(^{31}\)

The limitations of the study were family history of Parkinson’s was not included in the screening of subjects. Subjects from all socioeconomic classes could not be added due to lack of their prior exposure to a couple of odors that were included in the set of The Sniffin Sticks Test. An equal number of participants were not included in each group. Further, gender-based differences could not be ascertained.

**Conclusion**

The novelty of the study lies in screening the local population for Smell Identification Ability, the sniffing score. It is concluded that a considerable percentage of our population is suffering from the lower olfactory performance that goes unscreened. Hyposmia, if screened early, can predict the predisposition of subjects towards disorders in which neurodegeneration plays a crucial role. Hence, the biological ageing of these subjects is accelerated as compared to chronologically age-matched subjects with normosmia.

**Conflicts of Interest**

None.

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