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Research Article

Assessment of Single Nucleotide Polymorphism in the 5'-Flanking Region of Insulin-Like Growth Factor-I (IGF-I) Gene as a Potential Genetic Marker for Fertility in Holstein Dairy Cows

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ABSTRACT

Insulin-like growth factor-I (IGF-I) is one of the most important metabolic factors that plays a critical role in cow fertility. Recently, point mutation of IGF-I gene at nucleotide position 512 (C/T transition) within the 5′-untranslated region (5'-UTR) has attracted the most attention. It has previously been demonstrated that there was an important relationship between this type of mutation and IGF-I concentration in dairy cows serum. Hence, we investigate the relationship between polymorphism within 512 of the 5'-UTR of IGF-I gene and some reproductive parameters in Iranian Holstein dairy cows. Blood samples were collected from 60 multiparous cows with a history of desirable fertility (SPC<2; n=25) and undesirable fertility (SPC≥2; n=35) based on the previous lactation numbers. The results showed that higher percentage (65%) of cows with CC genotype had desirable fertility (SPC<2); while a lower percentage of cows with TC (33.3%) and TT genotypes (14.3%) had good fertility (P<0.05). Therefore, the CC genotype was associated (P<0.05) with desirable fertility. In addition, the IGF-I mutation had a significant effect on service per conception and days open in which cows with TT genotype and TC genotype had greater average of services per conception and days open compared to cows with the CC genotypes (P<0.05). It can be concluded that the C/T mutation within this region of IGF-I gene may influence the reproductive parameters in Holstein dairy cows. These data support the hypothesis that the mutation in this site might be considered as a genetic marker for reproductive performance in Holstein dairy cows.

Key Words: Insulin-like growth factor-I (IGF-I), polymorphism, fertility, dairy cow

ÖZET

SİYAH ALACA SIĞIRLARINDA İNSÜLİN BENZERİ BÜYÜME FAKTÖRÜ-I (IGF-I) GENİNİN 5'- SINIRDAŞ BÖLGESİNDEKİ TEK NÜKLEOTİD POLİMORFİZMİNİN FERTİLİTE İÇİN POTANSİYEL GENETİK MARKIR OLARAK DEĞERLENDİRİLMESİ

İnsulin benzeri büyüme faktörü-I (IGF-I) inek fertilitesinde kritik bir rol oynayan en önemli metabolik faktörlerden birisidir. Son yıllarda IGF-I geninin 5'- kodlanmayan bölgesinde (5'-UTR) 512. nükleotid pozisyonundaki (C/T dönüşümü) nokta mutasyonu oldukça ilgi çekmiştir. Bu tip mutasyon ile süt ineği serumundaki IGF-I konsantrasyonu arasında önemli bir ilişki bulunduğu bildirilmiştir. Bu nedenle İran Siyah Alaca sütçü ineğine ait bazı reprodüktif parametreler ile IGF-I geninin 5'-UTR bölgesinde 512. nükleotidindeki polimorfizm arasındaki ilişkiyi inceledik. Kan

örnekleri, daha önceki laktasyonlarında istenilen düzeyde fertilite gösteren (SPC<2; n = 25) ve göstermeyen (SPC≥2; n=35), daha önce buzağılamış toplam 60 adet inekten toplanmıştır. İneklerin yüksek bir yüzdesi (%65) CC genotipine ve istenilen fertilite düzeyine sahip oldukları (SPC<2); ineklerin daha düşük bir yüzdesinin de (%33) TC ve TT (%14,3) genotiplerine ve iyi fertiliteye sahip oldukları (P<0,05) tespit edilmiştir. Bu nedenle CC genotipi istenilen fertilite düzeyi ile bağlantılıdır (P<0,05). Ayrıca, IGF-I mutasyonunun gebelik başına tohumlama sayısı ve servis periyodu süresi üzerine önemli derecede etkili olduğu bulunmuştur. TT ve TC genotipine sahip ineklerin CC genotipine sahip olanlara göre daha yüksek gebelik başına tohumlama sayısı ve servis periyodu süresi ortalamasına sahip oldukları tespit edilmiştir (P < 0,05). Bu çalışmada sonuç olarak IGF-I geninin bu bölgesinde meydana gelen C/T mutasyonu Siyah Alaca ineklerde reprodüktif parametreleri etkileyebileceği sonucuna ulaşılmıştır. Elde edilen sonuçlar, bu bölgedeki mutasyonun Siyah Alaca ineklerde genetik işaretleyici olarak kullanılabileceği hipotezini desteklemektedir.

Key Words: İnsülin benzeri büyüme faktörü-I (IGF-I), polimorfizm, fertilite, süt ineği

Introduction

The main factors affecting fertility of industrial dairy cows include genetic, nutrition, management and milk production. Postpartum ovarian activity was impaired following hormonal and metabolic changes especially after calving and eventually the cattle's reproductive performance will be affected (Kawashima et al., 2007; Zulu et al., 2002). One of the most important metabolic factors affecting the reproductive activity is insulin-like growth factor-I (IGF-I) concentration changes after calving (Kadivar et al., 2012; Tamadon et al., 2011). Insulin-like growth factor-I is produced in organs of reproductive significance such as hypothalamus, ovaries, oviducts, and uterus (Daftary and Gore, 2005; Watson et al., 1999). It can change reproductive activity by affecting on neural pathway which control production of GnRH or effect on the secretion of pituitary gonadotropin; it has also direct effects on the ovary and influences its susceptibility to FSH and LH (Lucy, 2000). In addition, IGF-I can influence on the proliferation and differentiation of granulosa cell, postpartum follicular growth and consequently first ovulation of the dominant follicle, development of corpus luteum and preimplantation embryo development (Chase et al., 1998; Kawashima et al., 2007; Monget and Monniaux, 1995; Stefanello et al., 2006; Velazquez et al., 2005). Correspondingly, a positive relationship has been reported between reproductive performance and the concentration of IGF-I after calving in dairy cows (Tamadon et al., 2011; Velazquez et al., 2008; Zulu et al., 2002).

Insuline like growth factor-I is a small secreted peptide with 70 amino acid and molecular weight about 7500 Dalton. It is similar to the insulin molecule structurally and functionally. IGF-I production in various body tissues, especially in the liver is produced mainly by influenced growth hormone. IGF-I in the blood stream can control producing growth hormone with a negative feedback (Becker, 2001). This combination is one of the link mediators between nutrition and reproduction (Lucy, 2000). IGF-I gene is located on chromosome 5 in cattle. Heritability of IGF-I concentration in the blood is calculated of a 0.23 to 0.52 (Swali and Wathes, 2006). Although different polymorphisms have been reported in IGF-I gene so far (Kirkpatrick, 1992 and 1993; Lien et al., 2000), the point mutation (C/T transition) at nucleotide position 512 within the 5′-untranslated region (5'-UTR) has attracted the most attention (Hines et al., 1998; Siadkowska et al., 2006). This type of mutation was first identified by Ge et al. (2001). Recently, Maj et al. (2008) discovered a significant association between the IGF-I genotypes based on this region and the IGF-I blood level.

Accordingly, the present study was performed in order to investigate the relationship between polymorphism within the 5'-UTR of IGF-I gene and some reproductive parameters in Iranian Holstein dairy cows.

Materials and Methods

Animal and sample collection

This study was carried out on registered multiparous Iranian Holstein cows at the farm of Farzis milk and meat producing complex in Shiraz, Fars province, south of Iran. The cows were kept under the same weather and management conditions in a similar manner. Cows were fed standard rations (total mixed ration) including mainly alfalfa, corn silage, beet pulp, cotton seed, soybean, corn and barley. The cows were milked three times daily with the use of a pipeline milking machine. Oestrus was detected four times daily by visual detection. Cow was artificially inseminated (AI), 12 hours after heat detection. Pregnancy diagnosis was carried out by rectal palpation on day 45 after artificial insemination.

In this study, 60 high producing Holstein dairy cows with the history of distinct service pre conception in previous lactation and acceptable physical conditions were chosen. Average of service pre conception (SPC) for previous parities has been calculated based on the all previous lactation data within cow (n = 240). Then, cows were divided into two groups of desirable fertility based on the service per conception (SPC<2; n=25) and undesirable fertility (SPC≥ 2; n=35) groups.

The cows with 3 to 6 lactation number were selected in each group with approximately equal proportion. With regard to the effect of periparturient diseases on fertility, directly or indirectly, only cows calved normally and without peripartum diseases (dystocia, retained placenta, clinical hypocalcaemia and ketosis) in the previous parities were used in the study. Selection criteria for studied cows included acceptable body condition score and general health during the various production stages in previous lactation. Cows had an average daily previous lactations milk yield of 30 kg.

Blood samples (5 ml) were collected by caudal venipuncture from each animal into sample tubes containing the anticoagulant potassium ethylenediaminetetraacetic acid (EDTA K3E 15%, 0.12 ml; BD Vacutainer, BD Vacutainer systems, Plymouth, UK) and stored at -20 °C for subsequent DNA extraction.

Genomic DNA extraction

Total genomic DNA was extracted from blood using the DNeasy® Blood and Tissue Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. The extracted DNA was diluted to a working concentration of 10-20 ng/µl, and 2.4 µl of it was used as a template in PCR.

IGF-I polymorphism

The amplification of the 5'-flanking region of the IGF1 gene was carried out with primer sequences designed by Ge et al. (2001). In this method, the IGF1/SnaBI polymorphism was identified using the Amplification Created Restriction Site (ACRS) methods. The 249-bp fragment of the IGF-I gene was amplified using primers IGF677F:

5'-ATTACAAAGCTGCCTGCCCC-3', and IGF897R: 5'-ACCTTACCCGTATGAAAGGAATATACGT-3' (The underlined introduce a restriction site near the point mutation).

The following PCR conditions were applied to each assay; 50 mM KCl, 10 mM Tris-HCl (pH=9.0), 1.5 mM $MgCl_2$, 200 µM dNTPs, 10 pmol of each primer, and 1 U *Taq* DNA polymerase (Fermentas, USA) per 20 µl reaction using 2.4 µl of DNA extracted as template. PCR were carried out using a Bio-Rad thermocycler (Bio-Rad Laboratories Inc., Hercules, USA) with the following conditions: with the initial denaturation at 94°C for 5 min, followed by 35 cycles, denaturation at 94°C for 45 sec, annealing at 62°C for 1 min and extension at 72°C for 30 sec. A final extension at 72°C for 7 min at the end of the amplification cycles was included. Sterile water was used as the negative controls. The PCR products were analyzed by agarose gel 1.5%. The positive reaction products were used for enzymatic digestion by *Sna*BI (TAC↓GTA) restriction endonuclease.

Digestion of the products of RFLP-PCR with the *Sna*BI nuclease (Fermentas Inc., USA) was carried out in a mixture consisting of 10 µl

of the PCR product, 1.5 µl 10X Buffer Tango, 2µl (30 U) of the enzyme, and 1.5 µl dH_2O to a final volume of 15 µl. The reaction was at 37°C for 5 h followed by 20 min of inactivation at 65°C. The digested PCR products were analyzed by agarose gel 3% in 1 × Tris-Acetic Acid- EDTA (TAE) buffer. The gels were stained with ethidium bromide (0.5 µg/ml) and visualized under UV light on a transilluminator.

Statistical analysis

The results were analyzed from the aspect of relationship between the polymorphism within the 5'-UTR of IGF-I gene and some reproductive parameters (calving to first service interval, days open (DO) and service per conception (SPC), along with health card records, were calculated). The results obtained were subjected to statistical analysis by means of chi-square test for independence. Three categories of cow genotypes (TT, TC and CC) with desirable fertility (SPC<2) and undesirable fertility (SPC≥2) groups were tested for significant differences by chi-square test. Reproductive parameters were compared between cows with different genotypes by Kruskal–Wallis test. The statistical package SPSS for Windows was used (SPSS for Windows, version 15, SPSS Inc, Chicago, Illinois). Probability values of P≤0.05 were considered significant.

Results

Point mutation and marker genotyping showed that a transition of T to C was identified at 512 bp 5′ to the UTR region. Primer IGF897R introduced a *Sna*BI restriction site, which cut the fragment amplified from the T allele (using primers IGF677F and IGF897R) into two fragments (223 bp and 26 bp). The 223-bp fragment and the whole fragment (249 bp) can be distinguished by agarose gel (Figure 1). The smaller 26 bp DNA fragment tends to give diffuse bands through the agarose gel and will not obviously visible.

The CC genotype was associated (P<0.05) with desirable (good) fertility. Higher percentage (65%) of cows with CC genotype had desirable fertility (SPC<2); while a lower percentage of cows with TC (33.3%) and TT genotypes (14.3%) had good fertility (P<0.05; Table 1).

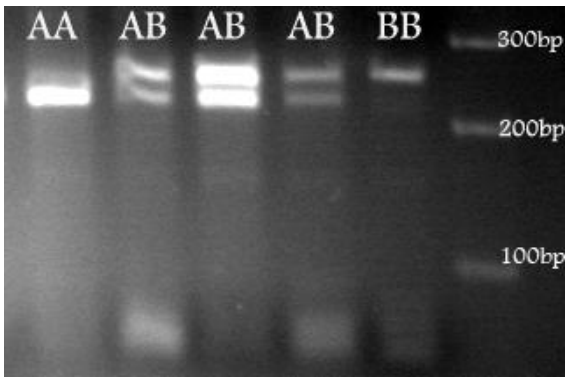

Figure 1. Electrophoresis pattern after digestion of the PCR products obtained from different IGF-I genotypes TT (AA), TC (AB), CC (BB).

Şekil 1. TT (AA), TC (AB) ve CC (BB) olmak üzere farklı IGF-I genotiplerinden elde edilen PCR ürünlerinin kesimi ile elde edilen elektroforez görüntüsü.

Table 2 sets out the results of the reproductive parameters data analysis. The IGF-I mutation had a significant effect on SPC and DO (Table 2), as cows with TT genotype and TC genotype had greater average of SPC and DO compared to cows with the CC genotypes (P<0.05; Table 2). No significant difference in the calving to first service was found between these genotypes (P>0.05).

IGF-I allele frequencies were 0.40 and 0.60 for T and C, respectively. The frequency of cows with TT, TC and CC genotypes were 11.7%, 55% and 33.3%, respectively. Observed and expected genotype number, allele frequency and chi-square test results are shown in Table 3.

Discussion

There is little and conflicting information available on polymorphisms in bovine IGF-I and their effects on reproductive performance in dairy cattle (Ruprechter et al., 2011). Several nucleotide sequence polymorphisms were identified in the bovine IGF-I gene (Ge et al., 2001; Kirkpatrick, 1992 and 1993; Lien et al., 2000). Recently, the C/T transition at position 512 of the 5'-UTR in IGF-I gene was shown to

be associated with blood IGF-I concentration in the Polish Holstein-Friesian cattle (Maj et al., 2008). The highest serum concentration of IGF-I in cows was found in CC genotype animals (1024 ng/ml) while TT and CT genotypes cows had 698 and 859 ng/ml in the serum, respectively (Maj et al., 2008). So, Maj et al. (2008) concluded that C/T transition in this region of IGF-I gene can influence the gene expression. Consequently, studying this polymorphism in relation to history of the reproduction may better reflect the effects of long term IGF-I exposure than studies on serum IGF-I concentrations, which may influence by various factors.

Table 1. Classification of IGF-I genotypes (TT, TC and CC) for cows with service per conception <2 (n=25) and ≥2 (n=35).

Tablo 1. Gebelik başına tohumlama sayısı <2 (n=25) ve ≥2 (n=35) olan inekler için IGF-I genotipleri (TT, TC ve CC).

Service per conception*	IGF-I Genotype %(N)		
	TT Genotype	TC Genotype	CC Genotype
< 2	14.3 (1) [b]	33.3 (11) [b]	65.0 (13) [a]
≥ 2	85.7 (6) [b]	66.7 (22) [b]	35.0 (7) [a]
Total	100.0 (7)	100.0 (33)	100.0 (20)

* Data are service per conception for previous lactations of dairy cows; N: number of cow.
[a,b] P<0.05, values within rows differ statistically.

Table 2. Comparison of the reproductive parameters (Mean ± SD) between different IGF-I genotypes of dairy cows.

Tablo 2. Sütçü sığırlarda farklı IGF-I genotiplerinin reprodüktif parametreler ile karşılaştırılması (Ortalama ± SD).

Reproductive parameters*	IGF Genotype		
	TT Genotype	TC Genotype	CC Genotype
Service per conception	2.35 ± 0.79[b]	2.29 ± 0.83[b]	1.77 ± 0.45[a]
Days open	114.05 ± 25.71[b]	116.46 ± 43.24[b]	93.92 ± 18.56[a]
Calving to first service	68.47 ± 5.54	74.67 ± 15.00	74.99 ± 13.33

* Mean ± SD include the reproductive parameters of the previous lactations of dairy cows.
[a,b] P<0.05, values within rows differ statistically.

Table 3. Observed and expected genotype number, allele frequency and chi-square test results.

Tablo 3. Gözlenen ve beklenen genotip sayıları, allel frekansları ve ki kare test sonuçları.

	Number of cow	
IGF Genotype	Observed	Expected
CC	20	20
TC	33	20
TT	7	20
Total	60	60

χ^2 = 16.9; df = 2; P = 0.0002; Allele frequency, C = 73; T = 47.

The present study describes a significant association between point polymorphism at this position and some reproductive performance. The results of this study showed that the cows with TT and TC genotypes needed more service per conception and had a longer calving to conception interval (days open) compared to those with the CC genotypes. Untranslated region (UTR) contains important information that required for the stability of mature mRNA and the regulation of translation value and protein synthesis with a mechanism of post-transcriptional regulation of gene expression (Kozak, 1991).

5'-UTR can also contain binding sites for transacting proteins, which can also modify the efficiency of mRNA translation. GC-rich region within 5'-UTR provided a capacity for mRNA to form stable stem-loop structure proximal to the 5'-cap. (Smith, 2008), In addition, the importance of 5′UTR SNP for translational regulation has been demonstrated in several disease in human (Cazzola and Skoda, 2000; Reynolds, 2002; Smith, 2008). It seems that de-regulation of translation, via the 5'-UTR sequences in TT and TC genotypes, is responsible for a significant reduction in IGF-I expression and associated to poor reproductive performance in dairy herds.

Ruprechter et al. (2011) have reported a higher frequency for the T allele (0.60) compared to the C allele (0.40) in Uruguay. They also reported that there was no effect of IGF-I genotype on some reproductive parameters (service per conception and pregnancy rate) as well as IGF-I concentration in none of the primiparous and multiparous Holstein cows (Ruprechter et al., 2011). In their study there was only a significant effect of IGF-I genotypes on calving-first service interval, in which primiparous cows with CC genotype had a longer interval than TC cows. While in our study Iranian Holstein cows showed a lower frequency for the T allele (0.40) compared to the C allele (0.60). Similarly, Bonakdar et al. (2010) and Mehmannavaz et al. (2010) have reported a lower frequency for T allele (0.438 and 0.463, respectively) in Iranian Holstein cow. In the present research, there was a significant effect of IGF-I genotypes on reproductive parameters, as cows with genotype CC had desirable fertility. It's worth mentioning that we used only cows calved normally and without peripartum diseases in the previous lactation. As cow selected based on the registered history, cow with the uterine infections and mastitis diseases in the previous lactation were excluded in our study. While in the study of Ruprechter et al. (2011) in Uruguay, they did not clarify used cows' conditions. Therefore, this discrepancy in the results may due to the variation in breed, the metabolic status and size group of cows which were used in the mentioned studies.

In Victorian dairy systems, plasma concentrations of IGF1 could be gradually altered by genetic selection (Stirling et al., 2009). IGF-I concentration was the main factor associated with earlier resumption of cyclic activity after calving (Kadivar et al., 2012). Cows with higher postpartum serum IGF-I concentrations show normal pattern of progesterone profile and better reproductive performance (Tamadon et al., 2011). Low concentrations of IGF-I before and after calving were associated with a failure to conceive in multiparous cows (Taylor et al., 2004). Taylor et al. (2004) reported that the likelihood of conception was increased by the increasing levels of IGF-I concentrations in the week after calving and at first service. Cows with higher plasma IGF-I at any time (28-21 prepartum days, 70-84, 120 – 182 and 210-271 postpartum days) tended to have a shorter interval to first ovulation after calving (Moyes et al., 2004). Here it is important to highlight that post calving peripheral IGF-I levels are affected by breed/genotype (Roberts et al., 2005; Spicer et al., 1993).

We found evidence for a significant association between C to T mutation in position 512 of IGF-I gene and the reproductive performance in dairy cows in Iran. The results showed that higher percentage (%65.0) of cows with genotype CC had good fertility, while a lower percentage of cows with genotype CT (%33.3) and TT (%14.3) had good fertility. In conclusion, C/T transition within 512 region of IGF-I gene may influence the reproductive parameters in Iranian Holstein dairy cows. These data support the hypothesis that the mutation in this site might be considered as a genetic marker for reproductive performance in Holstein dairy cows.

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