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L-carnitine and its functional effects in poultry nutrition

SH. GOLZAR ADABI[1]*, R.G. COOPER[2], N. CEYLAN[1] and M. CORDUK[1]

[1]Faculty of Agriculture, Department of Animal Science, Ankara University, Diskapi, Ankara, 06110-Turkey; [2]Physiologist, (formerly University of Zimbabwe), 22 Kimble Grove, Pype Hayes, Birmingham B24 0RW, UK
*Corresponding author: adabishahram@gmail.com

L-carnitine has indispensable functions in intermediary metabolism and is received by endogenous synthesis and from exogenous sources. It plays an obligate role in fatty acid metabolism by directing fatty acids into the mitochondrial oxidative pathway through the action of specialised acyltransferases. In poultry production, L-carnitine has a multi functional purpose, which includes: growth promotion, strengthening the immune system, antioxidant effects and improving semen quality. The concentration of L-carnitine in animals varies widely across species, tissue type, and nutritional status of the animal. It has been suggested that the L-carnitine requirement may be increased under certain circumstances such as via higher performance, various stress conditions and where the diet is deficient in animal protein sources. The review of L-carnitine functions uniquely includes the main aspects of this consequential feed supplementary inclusion in poultry nutrition.

Keywords: chicken; L-carnitine; performance; immune response; antioxidation; fertility

Introduction

Continuous selection of broilers and layers for better feed efficiency and egg production is aligned with an alteration of nutrient requirements. As a result, some of the nutrients previously considered as non-essential may become essential. Therefore, re-evaluating the L-carnitine requirement of poultry has become a necessity. During the past two decades there have been more than 70 articles published dealing specifically with L-carnitine application on poultry production, but there are contradictory reports. For example, 17 studies found no effect of L-carnitine on performance of birds, although almost 14 studies noticed that growth rate improved by L-carnitine feeding. It is timely that these conflicting reports are collated and reviewed. It is not the intention of this review to discuss in detail the chemistry, structure and synthesis of L-carnitine, as this has already been completed (Bremer, 1962, 1983; Borum, 1983; Bieber, 1988). The aim of this article is to provide a review of the important applications in poultry production by emphasizing the current knowledge of the importance of L-carnitine in poultry nutrition,

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and to provide useful information for researchers and students. The nutritional functions of L-carnitine will add to the few available review articles of the poultry industry.

A brief history and chemistry of L-carnitine

L-carnitine ($C_7H_{15}NO_3$) (*Figure 1*) is present in both plasma and tissue as free carnitine, or bound to fatty acids as acyl carnitine derivatives (Tomita and Sendju, 1927; Bieber, 1988). It is a water soluble zwitterionic compound (161.2 M_R). It has been recognized to be physiologically important for nearly a century; yet, its fundamental roles in some aspect such as health and disease remain to be fully understood (Mast *et al.*, 2000).

Due to its asymmetric structure at carbon two, the molecule possesses optical activity and exists in two enantiomeric forms. The D-form does not occur in nature but may be obtained by chemical synthesis (Liedtke *et al.*, 1982) and only the L-form is biologically active and occurs in nature and it has pharmacological and nutritional properties (Mardones *et al.*, 1999). However, subsequent investigations have shown that D-Carnitine acts as a competitive inhibitor of active uptake systems for the L isometric form (Walter and Schaffhauser, 2000).

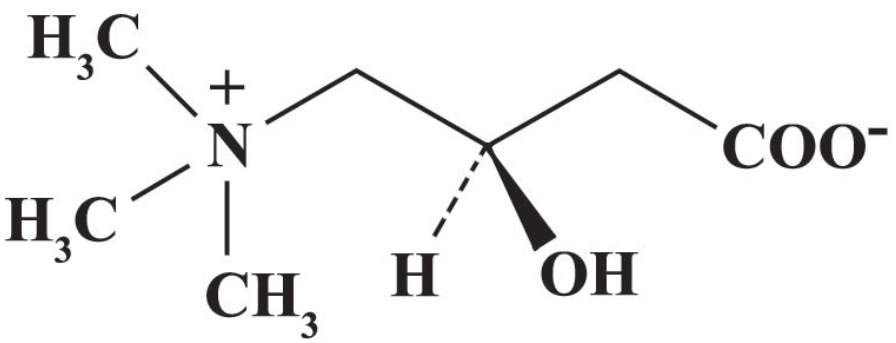


Figure 1 Structural formula for L-carnitine (L-3-hydroxy-4-N-trimethylaminobutyrate) (Metzler and Metzler, 2003).

Synthesis and deficiency of L-carnitine

The first convincing evidence for carnitine biosynthesis in animals was obtained from chick embryos, which contained significant amounts of carnitine. None was found in eggs (Bremer, 1983). Endogenous biosynthesis (in the kidney, liver and brain) occurs in small amounts, but appears sufficient to cover normal requirements. However, this is not the case in neonates (Borum, 1983; Rebouche, 1992; Keralapurath *et al.*, 2010a), where birds are under conditions of stress, higher performance and diets rich in fat (Rebouche and Paulson, 1986; Rebouche, 1992; Rabie and Szilagyi, 1998; Harpaz *et al.*, 1999).

Two essential amino acids (lysine and methionine), three vitamins (ascorbate, niacin in the form of nicotin amide adenine dinucleotide and vitamin B_6), and reduced iron (Fe^{2+}) are required as cofactors for the enzymes involved in the metabolic pathway of L-carnitine synthesis (Borum, 1983; Rebouche, 1992; Leibetseder, 1995). Reports of nutritional L-carnitine deficiency are rare (Harpaz, 2005), and accumulation of toxic acyl-coenzyme (CoA) metabolites in mitochondria due to L-carnitine deficiency impair

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the citrate cycle, gluconeogenesis and fatty acid oxidation (Knuttel-Gustavsen and Harmeyer, 2007; Harpaz, 2005).

Bioavailability and absorption of L-carnitine

Mechanisms of the absorption of L-carnitine in the small intestine have not yet been completely clarified (Fischer *et al.*, 2009). Some reports have suggested that both, active (dependent on Na^+) and passive mechanisms are involved in intestinal L-carnitine transport (Shaw *et al.*, 1983; Matsuda *et al.*, 1998; Garcia-Miranda *et al.*, 2005). More recently, functional and molecular studies revealed that L-carnitine crosses the intestinal apical membrane by an active, Na^+-dependent and electrogenic transport system that resembles the organic cation/carnitine transporter (OCTN2) which is a member of the solute carrier 22A gene family, localised on the apical membrane of cells (Kato *et al.*, 2006). Another transporter that may be involved in the intestinal absorption of L-carnitine is $ATB^{0,+}$ (the sodium- and chloride-coupled amino acid transporters). $ATB^{0,+}$ is already known as a high-affinity transporter of cationic and neutral amino acids that also functions as a low-affinity/high-capacity transporter for carnitine (Nakanishi *et al.*, 2001; Hatanaka *et al.*, 2004).

General functions of L-carnitine

Although L-carnitine participates in several metabolic reactions, its most widely known function is probably interference in the overall context of normal fatty acid metabolism (Zeyner and Harmeyer, 1999; Hoppel, 2003). A major factor controlling the oxidation of fatty acids is the rate of entry into the mitochondria. While some long-chain fatty acids (perhaps 30% in total) enter mitochondria and are converted to CoA derivatives in the matrix, the majority are 'activated' to acyl-CoA derivatives on the inner surface of the outer membranes of the mitochondria (Metzler and Metzler, 2003). L-carnitine serves as the carrier that transports activated long chain fatty acyl groups across the inner mitochondrial membrane. L-carnitine acyl transferases are able to reversibly transfer an activated fatty acyl group from CoA to the hydroxyl group of carnitine to form an acylcarnitine ester. The reaction is reversible, so that the fatty acyl CoA derivative can be regenerated from the carnitine ester. Carnitine palmitoyl transferase I (CPTI; also called carnitine acyltransferase I, CATI), the enzyme that transfers long-chain fatty acyl groups from CoA to carnitine, is located on the outer mitochondrial membrane (*Figure 2*). Fatty acylcarnitine crosses the inner mitochondrial membrane with the aid of a translocase. The fatty acyl group is transferred back to CoA by a second enzyme, carnitine palmitoyl transferase II (CPTII or CATII). The carnitine released in this reaction returns to the cytosolic side of the mitochondrial membrane by the same translocase that brings fatty acylcarnitine to the matrix side. Long-chain fatty acyl CoA, now located within the mitochondrial matrix, is a substrate for β-oxidation (Smith *et al.*, 2004).

Another function of L-carnitine is metabolic function, in this case L-carnitine act as a buffer for excess acyl residues. This function of L-carnitine beneficial effects to the cell, *e.g.,* by elevating the mitochondrial acetyl-CoA/CoA ratio. Sufficiently high concentrations of free CoA are required to keep the substrate flux of the citric acid cycle at a high level (Zeyner and Harmeyer, 1999).

A study conducted by Owen *et al.* (2001) showed that supplementation of the pigs' diet with L-carnitine increased protein accretion. Branched chain keto acids (BCKA) are derived from transamination of branched-chain amino acids (BCAAs; valine, leucine,

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and isoleucine) by BCAA transaminase (Misra *et al.*, 2004). L-carnitine has also ability to enhance the oxidation of these derivatives and its effect was markedly dependent on its concentration (Van Hinsbergh *et al.*, 1980). L-carnitine can interfere in the oxidation of BCKA (Hoppel, 2003). Paul and Adibi (1978) concluded that L-carnitine stimulates decarboxylation of BCAA by increasing the conversion of their ketoanalogues into carnitine esters.

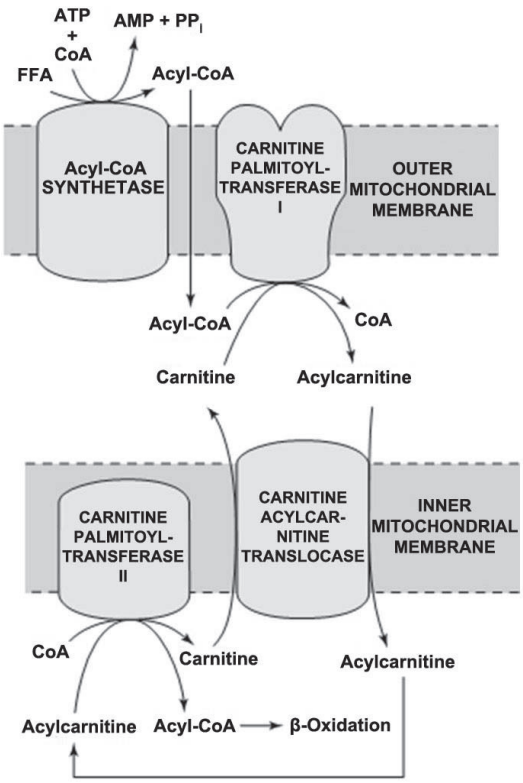


Figure 2 Role of L-carnitine in the transport of long-chain fatty acids through the inner mitochondrial membrane. Long-chain acyl-CoA can not pass through the inner mitochondrial membrane, but its metabolic product, acylcarnitine, can (Murray *et al.*, 2003).

Effect of L-carnitine on poultry

Before addressing the topic, a summary of some researches which are related to nutritional effects of L-carnitine supplementing in poultry diet and their brief results has been shown in (*Table 1*).

PERFORMANCE

Feed efficiency remains the most important trait in commercial animal breeding programs, as feed represents 60-70% of the cost of raising an animal to market weight. As mitochondria are responsible for producing 90% of cellular energy, some of the variations in broiler growth performance and phenotypic expression of feed

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efficiency may be due to differences or inefficiencies in mitochondrial function (Bottje *et al.*, 2002). As it mentioned previously, L-carnitine is attributed to an increase in utilization of energy as a result of the increase in fatty acid oxidation by the mitochondria (Bremer, 1962; 1983). Some publications seek to justify the use of L-carnitine in the diet of poultry by claiming that L-carnitine has benefical effects on performance, although researchers differ in their opinion of the magnitude or existence of such benefits in published reports.

There was no noticeable influence of L-carnitine supplementation on live weight, feed consumption or feed conversion ratio in broilers (Cartwright, 1986; Leibetseder, 1995; Buyse *et al.*, 2001; Lien and Horng, 2001; Xu *et al.*, 2003; Cevik and Ceylan, 2005; Kidd *et al.*, 2005; Golzar Adabi *et al.*, 2006b; Buyse *et al.*, 2007; Corduk *et al.*, 2007; Kidd *et al.*, 2009; Keralapurath *et al.*, 2010a,b). This was also the case for broiler and turkey (Barker and Sell, 1994). There was no variation in body weight in hatching chicks (Zhai *et al.*, 2008a), in laying hens (Deng *et al.*, 2006, Ghods-Alavi *et al.*, 2010), in ducks (Arslan *et al.*, 2003), and in Japanese quails (*Coturnix coturnix*) (Arslan *et al.*, 2004a, Sarica *et al.*, 2005 and 2007).

However, Buyse *et al.* (2001) concluded that lack of L-carnitine effects on broiler performance did not mean that L-carnitine supplementation cannot have beneficial effects in other circumstances. In view of the elevated proportional heart weights with addition of 100 mg/kg L-carnitine to basal diet, it can also be argued that L-carnitine is a potential agent for reducing the incidence of metabolic diseases in broiler chickens.

In contrast, studies on pigeons (Janssens and De Wilde, 1994; Janssens *et al.*, 2000a; Janssens *et al.*, 1999), native Turkish geese (Arslan *et al.*, 2004b), pheasant (Suchy *et al.*, 2008), broiler chickens and laying hens (Lettner *et al.*, 1992; Rabie *et al.*, 1997a,b,c; Rabie and Szilagyi, 1998; Rodehutscord *et al.*, 2002; Kita *et al.*, 2002; Golzar Adabi *et al.*, 2006a; Geng *et al.*, 2007; Nouboukpo *et al.*, 2010) noticed improved live weight, feed consumption, feed conversion efficiency or egg production by feeding dietary L-carnitine.

A diet of 50 mg/kg dietary L-carnitine in broiler chicks from 0-3 week of old, resulted in an improved feed conversion ratio (Cevik and Ceylan, 2005). Considering this and similar reports it would appear that using L-carnitine during early stages of growth in poultry has a better effect on performance (Rabie and Szilagyi, 1998; Kita *et al.*, 2002).

No benefits due to L-carnitine supplementation on egg production was observed by Rabie *et al.* (1997c), Corduk *et al.* (2008), Zhai *et al.* (2008b), Ghods-Alavi *et al.* (2010). In contrast, Golzar Adabi *et al.* (2006a, 2007) in an experiment with broiler breeders hens that lasted from 29-34 weeks, found that L-carnitine had no effect on egg production of broiler breeder hens except at 33 and 34 weeks of age ($p<0.01$). In a study with black neck ostriches determined that the supplementary diet with 500 mg/kg L-carnitine increased ($P<0.01$) the egg production percentage (Hajibabaei *et al.*, 2008). There are some hypotheses about mode of action of L-carnitine in improvement of the growth performance that can be summarised as thus. The improvements in body weight gain of broilers observed in some studies due to added dietary L-carnitine may be attributable to an improved utilization of dietary nitrogen, achieved through more efficient fat oxidation by L-carnitine. The increased fatty acid oxidation induced by L-carnitine may result in decreased availability of long-chain fatty acids for esterification to triacylglycerols, and at the same time can raise the mitochondrial level of acetyl-CoA. Such a situation can affect the activity of pyruvate carboxylase, which is an acetyl-CoA-dependent enzyme that can supply carbon chains for amino acid biosynthesis (Cyr *et al.*, 1991).

Enhanced growth by additional carnitine maybe partially associated with its amino-acid-sparing function in addition to its role in fatty acid metabolism. Theoretically, an exogenous carnitine supply can decrease the need for biosynthesis of carnitine from

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methionine, thus sparing methionine for other biological functions (La Count *et al.*, 1995). Indeed, addition of carnitine to low protein diets did have a methionine-sparing effect and promote growth in rats (Khairallah and Wolf, 1965). An increased supply of carnitine has been shown to spare branched-chain amino acids from oxidation in tissues (Owen *et al.*, 1996).

Another hypothesis concerns the positive effect of L-carnitine on performance (Kita *et al.*, 2002). It is known that insulin-like growth factors (IGFs) stimulate growth rate in a number of animal species (Beccavin *et al.*, 2001), Kita *et al.* (2002) found that when dietary L-carnitine concentrations were increased from 0 to 1000 mg/kg in an adequate protein diet (200 g/kg), plasma IGF-I concentrations were increased (a 70 amino acid peptide) having the potency to stimulate body weight gain (Kita *et al.*, 2005) and thereby growth of chicken was improved.

As previously mentioned, discrepancies in growth performance in response to additional dietary L-carnitine may result from different levels of L-carnitine supplementation, L-carnitine level of basal diet, nutritional and physiological status of the animal, the nutrient composition of their diets (such as dietary lipid and protein intake, supply or absence of essential amino acids), the possible effects of enzymatic breakdown of branched chain amino acids, sparing effects of L-carnitine and its considerable precursors (lysine and methionine), interspecies differences, age, sex, feeding programme, and managerial or environmental conditions of the animals (Rabie *et al.*, 1997c; Owen *et al.*, 2001; Rodehutscord *et al.*, 2002; Xu *et al.*, 2003; Celik and Ozturkcan, 2003). Fischer *et al.* (2009) recently documented that the reason for these contradictory results is unknown.

ABDOMINAL FAT

Determining abdominal fat weight as a predictor of total body fat in poultry (Sonaiya, 1985) in feeding studies is a well established methodology. In some feeding trials with L-carnitine there have been statistical differences in both abdominal and mesenterical fat percentage, meaning that the L-carnitine group produced lower levels of body fat compared to the control group (Rabie *et al.,* 1997a; Rabie and Szilagyi, 1998; Buyse *et al.,* 2001; Xu *et al.,* 2003; Kidd *et al.,* 2005; Ghods Alavi *et al.,* 2010). However other studies have shown no beneficial effects of L-carnitine supplementation of diets of pigs, broilers or turkeys relative to utilization or deposition of fat (Benevenga *et al.,* 1989; Barker and Sell, 1994; Leibetseder, 1995). Some researchers found a higher fat level in the breast of 150 mg/kg L-carnitine supplemented group than the 50 and 100 mg/kg groups ($p<0.05$) (Cevik and Ceylan, 2005).

The L-carnitine effect on decreasing abdominal fat concurs together with the L-carnitine role in biological systems. Theoretically, diets supplemented with L-carnitine, therefore, should enhance the oxidation of these fatty acids, thereby decreasing their availability for esterification to triacylglycerols and storage in the adipose tissues (Bremer, 1983; Lien and Horng, 2001; Xu *et al.,* 2003).

ALBUMEN HEIGHT AND HAUGH UNIT SCORE OF EGG

Rabie *et al.* (1997c) reported that improvements in albumen height and Haugh unit score of eggs laid by L-carnitine supplemented hens may be due to the higher metabolic rate in the magnum and/or higher activity of the shell gland. Optimum activity of shell glands of uterus may result in the better integrity of eggshells, consequently lower carbon dioxide (CO_2) evaporation from eggshell pores. Beside of this effect, it appears that L-carnitine may play a role in the synthesis or secretion of β-ovomucin by promoting metabolic rate in the magnum (Peebles *et al.*, 2007; Zhai *et al.*, 2008b; Daskiran *et al.*, 2009). As reported previously the quality of the albumen is largely dependent on the

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amount of ovomucin, particularly β-ovomucin, secreted by the magnum. It is reported that β-ovomucin is mainly responsible for the gelatinous properties of the thick albumen gel (Robinson, 1987; Kita *et al.,* 2005; Daskiran *et al.*, 2009) . Improvements in albumen height and Haugh unit score of eggs was also observed by Kita *et al.* (2005); Rezaei *et al.* (2008) and Ghods Alavi *et al.* (2010).

EFFECT OF L-CARNITINE ON IMMUNITY OF POULTRY

Interestingly, the selection of today's modern chickens for growth and egg production has resulted in diminished inflammatory response, but selection for more robust immune responses results in diminished growth and egg production. It has recently been proposed that certain nutrients can be used as a means to specifically prevent infectious diseases in poultry (Kogut, 2009). Besides taking part in the transfer of long-chain fatty acids, early experiments have demonstrated the immune-modulating properties of L-carnitine (De Simone *et al.,* 1982; Famularo and De Simone, 1995). Leghorn-type chickens offered the 1000 mg/kg in feed had a higher ($p<0.05$) primary antibody level against sheep red blood cells (SRBC) than either of the other two groups (0 and 100 mg/kg) at week 12. These birds had a higher ($p<0.05$) relative thymus weight than the control at week 12 (Deng *et al.,* 2006). Similarly, Golzar Adabi *et al.* (2006b) reported that the addition of 100 mg/kg L-carnitine to a broiler diet caused significantly ($p<0.05$) higher antibody response to SRBC and Newcastle disease virus ($p<0.01$) than non-treated birds. Furthermore, additional dietary 100 mg/kg L-carnitine had the highest bursa of fabricius, spleen ($p<0.05$) and thymus weight ($p<0.01$) by comparison with the other groups (0, 25 and 75 mg/kg L-carnitine in diet, respectively). Buyse *et al.* (2007) confirmed that 100 mg/kg L-carnitine in the diet of broiler chickens modulates the innate immune response in terms of an enhanced acute phase protein response and L-carnitine has glucocorticoid-like effect.

With regard to the role of L-carnitine in cellular immunity, it was present in lymphocytes at high concentrations, and inhibited apoptosis of those immune cells (Famularo and De Simone, 1995; Moretti *et al.,* 1998) and enhanced their proliferative response to mitogens (De Simone *et al.,* 1994). Furthermore, higher levels of antibodies specific to influenza and pneumococcal vaccines were produced in L-carnitine-supplemented mice (Shug and Gravenstein, 1996). Dietary L-carnitine supplementation significantly ($p<0.05$) increase total Ig G and Ig A but not Ig M responses after both primary and the secondary immunisation with bovine serum albumin in broilers (Mast *et al.,* 2000). Supplementation increased the primary bovine serum albumin specific Ig G and Ig M responses in pigeons (Janssens *et al.,* 2000b). To explain the impact of L-carnitine on the bovine serum albumin-specific serum Ig level, several possibilities are available: enhancement of lymphocyte activation or proliferation, an increased lifetime span of the lymphocytes, or a combination of these mechanisms.

There is, however, paucity of research reports delineating specific requirement estimates of L-carnitine for a given immune function in poultry. The mode of immuno-modulation by L-carnitine is not clear, but modified metabolism of lipids (La Count *et al.,* 1995) and enhanced secretion of hormones, such as insulin, insulin-like growth factor-I (Musser *et al.,* 1999) and tri-iodothyronine (T_3) (Buyse *et al.,* 2001) may be involved, along with several lipids (Miles and Calder, 1998) and hormones (Marsh, 1994) are immuno-modulators and some researchers such as Liu *et al.* (2004) believe that L-carnitine and some of its acyl esters act as very potent reactive oxygen species scavengers and are known to have immuno-modulary properties in mammalian as well as in avian species (Buyse *et al.*, 2007).

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ANTIOXIDANT EFFECT OF L-CARNITINE IN POULTRY

Oxidative stress constitutes an important mechanism that leads to biological damage, and it is regarded as one of the causes of several pathologies that affect poultry growth (Fellenberg and Speisky, 2006). The main free radicals are those species which superoxide anion (O_2^{-}•) and hydroxyl radical (HO•) derived from oxygen, and nitric oxide (NO•) derived from nitrogen, but non free-radical species are H_2O_2 and singlet oxygen (O_2). These various forms of activated oxygen can cause oxidative damage in tissues and cells (Surai *et al.,* 1998; Fellenberg and Speisky, 2006; Gulcin, 2006). For provide defences against free radicals body is naturally produced antioxidant enzymes, such as: glutathione peroxidase, glutathione reductase, catalase, thioredoxin reductase, superoxide dismutase, haem oxygenase and biliverdin reductase (Gulcin, 2006). Besides these enzymes, diet can be used as a vehicle to provide compounds with antioxidant properties as they have special place in the maintenance of high production performance in poultry (Surai, 2007). The antioxidant role of dietary L-carnitine has been studied extensively in the last 15 years. Mode of antioxidant effect of L-carnitine can be summarized as following:

L-carnitine prevents oxidative stress and regulates nitric oxide, the cellular respiration (Brown, 1999) and the activity of enzymes involved in defence against oxidative damage (Kremser *et al.*, 1995).

L-carnitine acts as an antioxidant in the protection of glutathione peroxidase, catalase and superoxide dismutase enzymes from further peroxidative damage (Kalaiselvi and Panneerselvam, 1998).

L-carnitine may have functions associated with scavenging of free radicals in cellular sites (Kalaiselvi and Panneerselvam, 1998; Atroshi *et al.,* 1999; Rani and Panneerselvam, 2002; Citil *et al.,* 2005).

L-carnitine supplementation has improved the glutathione and total thiol (-SH) status. L-carnitine has been shown to exert thiol and methionine sparing activity, and it is suggested it can be improved the antioxidant status in tissues, since L-carnitine increases glutathione peroxidase (GSH) levels (Di Giacomo *et al.,* 1993; Kalaiselvi and Panneerselvam, 1998).

L-carnitine is associated with buffering of excess acetyl-CoA, which in itself can cause free radicals formation and potentially toxic to the cells, and it was reported that L-carnitine has a protective effect on lipid peroxidation by reducing the formation of hydrogen peroxide (Agarwal and Said, 2004; Bayraktar *et al.,* 2008).

The production of highly reactive oxygen species is catalysed by free iron through Haber-Weiss reaction (Haber and Weiss, 1934). L-Carnitine and its esters inhibits the microsomal peroxidation and it has a role in chelating free Fe^{2+} ions available for ascorbic acid to induce lipid peroxidation and by this way it reduces free radical generation (Arduini, 1992; Kalaiselvi and Panneerselvam, 1998; Dayanandan *et al.,* 2001).

L-carnitine could prevent oxidative damage by increasing oxygen utilization and protecting from adenosine triphosphate (ATP) depletion (Di Giacomo *et al.,* 1993).

By its shuttle effect in the outer mitochondrial membrane (Bremer, 1983; Borum, 1987; Rebouche, 1992; Mast *et al.,* 2000), L-carnitine profoundly influences both skeletal muscle and myocardial fatty acid oxidation, and maintains low pools of fatty acid (acyl)-coenzyme A compounds, which are potentially toxic (Bremer, 1962, 1983).

EFFECT OF L-CARNITINE ON REPRODUCTION

A major component of broiler industry success has been the improvement in efficiency reached due to genetic selection programs applied to the parental stock. The industry anticipates that genetic improvement will continue with birds growing faster and yielding

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more meat. However, it is recognized that this intense selection has been accompanied by reduced reproductive efficiency and a fertility decline likely due to subfertile males within breeder flocks, to the point that male fertility may potentially become a limiting factor for growth of the broiler industry in the near future (Reddy and Sajadi, 1990; Barbato, 1999). The precise causes of this fertility reduction have not been yet determined, although it has been suggested to be related to the changes in male physical conditions and behaviour, both of which that may have impaired male vigour and mating ability.

The sperm plasma membrane plays a very active function in sperm fertilisation capacity (Lenzi *et al.*, 1996). Since the 19th century, many researchers have reported that lipids contributing to the membrane structure of spermatozoa have a major role in the metabolism, cold sensitivity, motility and viability of spermatozoa and their ability to fertilise the female gamete (Kelso *et al.,* 1997; Surai *et al.,* 1998). In many animal species, the major lipid components of spermatozoa membrane are phospholipids, and they contain extremely high amounts of poly unsaturated fatty acid (PUFA) (Kelso *et al.,* 1997; Surai *et al.,* 1998). Therefore, spermatozoa are more susceptible to reactive oxygen species (ROS) induced damage because of abundant mitochondria in the middle-piece and high concentrations of PUFA in the membrane (Fujihara and Koga, 1984; Surai *et al.,* 1998; Sanocka and Kurpisz, 2004).

The presence of high concentrations of long chain PUFA in the lipid structure of sperm cells requires efficient antioxidant systems to protect against peroxidative damage and sperm dysfunction (Alvarez and Storey, 1989). In most experiments, researchers generally agree on the beneficial effects of L-carnitine on poultry fertility. L-carnitine does this by increasing sperm quantity and quality. It is necessary to mention that L-carnitine can be removed from blood and released into epididymal lumen by active transporters (Enomoto *et al.,* 2002; Kobayashi *et al.,* 2005) which are regulated by androgens (Cooper *et al.,* 1986a,b) and ultimately transported into spermatozoa (Jeulin and Lewin, 1996).

The *ad libitum* consumption of 500 mg/kg (Neuman *et al.,* 2002) or 125 mg/kg (Zhai *et al.,* 2007) of dietary L-carnitine to white leghorn roosters increased sperm concentration and reduced sperm lipid peroxidation. In a study with mature male Japanese quail breeders Sarica *et al.* (2007) reported that the supplementation of dietary L-carnitine at levels of 250 or 500 mg/kg to a basal diet significantly increased sperm viability of the mature male Japanese quail breeder. In another study conducted by Golzar Adabi *et al.* (2007) semen quantity and quality significantly ($p<0.01$) increased in L-carnitine-fed broiler breeders. L-carnitine treated ostriches (250 and 500 mg kg^{-1}) have increased sperm count, sperm motility, live sperm ($p<0.05$) (Golzar Adabi *et al.,* 2008).

Possible mechanisms for these effects can be summarised as follows. Based on the knowledge of the action of L-carnitine on cellular energy metabolism and on its anti-apoptotic effect, L-carnitine contributes directly in sperm motility and may involve in successful maturation and metabolism of spermatozoa (Lenzi *et al.,* 2003; Agarwal and Said, 2004; Lenzi *et al.,* 2004; Balercia *et al.,* 2005). As the level of free L-carnitine in seminal plasma declines, the process of β-oxidation in sustentacular cells decreases, which may lead to a reduction of energy-dependent and can cause sperm function, such as motility and movement capacity, to be significantly decreased.

A direct effect of L-carnitine on the functionality of sertoli cells is also plausible, as observed by Palmero *et al.* (2000) and Caviglia *et al.* (2004). These researchers reported an increase in lipid oxidation, glycolysis, and expression of specific proteins involved in the regulation of insulin-like growth factor (IGF) activity and glucose utilization by *in vitro* cultured sertoli cells in response to L-carnitine. They concluded that the

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improvement in semen quality reported after *in vivo* treatments could be related to its interactions with sertoli cell functions.

Intra cellular production of ROS results in the immediate accumulation of lipid peroxides in the plasma membrane and cytosol of cells (Aitken *et al.,* 1993) and induces DNA damage in the sperm nucleus and mitochondria (Aitken *et al.,* 2010). This accretion has been correlated with the impaired ability of sperm to partake in the acrosome reaction and sperm-oocyte fusion and maybe responsible for a reduction in motility and capacity for fertilisation (Aitken *et al.,* 1993; Aitken *et al.,* 2010). L-carnitine, through its antioxidant properties, has been shown to increase the activity and levels of antioxidant enzymes, like SOD may protect sperm membranes from toxic oxygen metabolites and protect the cell normal morphous and physiologic function (Kalaiselvi and Panneerselvam, 1998; Neuman *et al.,* 2002; Zhai *et al.,* 2007).

Testicular multinucleated giant cells are described as a 'degenerative syndrome' resulting presumably from the inability of tetraploid primary spermatocytes to complete meiotic division; thus, maturation arrests at the spermatid stage of development (Corrier *et al.,* 1985; Neuman *et al.,* 2002; Sarica *et al.,* 2007). Multinucleated giant cells consist primarily of aggregates of degenerated spermatocytes and spermatids and are often sloughed into the lumen of seminiferous tubules (Sur *et al.,* 1997; Neuman *et al.,* 2002; Sarica *et al.,* 2007). It has been reported that dietary L-carnitine decreased multinucleated giant cells per testes both in white leghorn roosters and mature quails (Neuman *et al.,* 2002; Sarica *et al.,* 2007). Roosters consuming 125 and 500 mg/kg dietary L-carnitine (Zhai *et al.,* 2007; Neuman *et al.,* 2002 respectively) significantly ($p<0.01$) decreased malonaldehyde production per billion sperm, which is the primary stable by-product of lipid peroxidation. Additionally, these results emphasize antioxidant properties of L-carnitine that may preserve sperm membranes in cocks, thereby extending the life span of sperm.

L-carnitines protective role is further sustained by accelerating repair processes following physical (Amendola *et al.,* 1991; Ramadan *et al.,* 2002) and chemical (Palmero *et al.,* 1990) damages on the testicular parenchyma.

EFFECT OF L-CARNITINE ON EMBRYONIC GROWTH AND HATCHABILITY

All nutrients needed for embryogenesis are provided by the hen by the time the fertile egg is laid (Buyse *et al.,* 2001). If nutritional deficiencies occur during the formation of the egg, it can have significant repercussions on the developing embryo (Moran, 2007). Hen diets are composed mainly of corn and soy, which contain low levels of L-carnitine (Buyse *et al.,* 2001). Therefore, eggs contain little or no L-carnitine (Chiodi *et al.,* 1994). Although L-carnitine biosynthesis increases during embryonic development, its levels are still much lower than those measured in adults because of the low activity of γ-butyrobetaine hydroxylase, the essential enzyme that catalyzes γ-butyrobetaine to L-carnitine (Borum, 1983; Rebouche, 1992). For this reason, it is thought that the chick embryo may have limited capability for *de novo* synthesis of L-carnitine during incubation (Casillas and Newburgh, 1969). Due to the limited ability of young chicks to synthesise L-carnitine, supplementation to the diet at hatch may have prolonged beneficial effects to the chicks. Conversely, yolk lipids provide essential energy to growing embryos. In fact, approximately 90% of the total energy requirement of the developing embryo is derived from fatty acid oxidation of yolk lipids (Noble and Cocchi, 1990). In other words, approximately 50% of the initial yolk lipids oxidized for energy production; the other 50% is incorporated into the body tissue and residual yolk of hatchlings (Lin *et al.,* 1991).

Chick embryonic tissues contain high levels of PUFAs (Noble and Cocchi, 1990;

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Speake *et al.,* 1998). PUFAs are susceptible to lipid peroxidation caused by free radicals, which are produced by *mitochondria* because of the high metabolic rate of rapidly developing embryos (Surai, 1999). Oxidative stress stimulates free radical generation by an increased electron leakage from mitochondria electron transport system. Over-production of free radicals results in impaired intracellular milieu and disturbed metabolism in embryos (Guerin *et al.,* 2001; Agarwal *et al.,* 2005). As mentioned previously, L-carnitine work as an antioxidant to scavenge free radicals and supplementation of hen's diets increases egg yolk L-carnitine concentrations (Leibetseder, 1995; Golzar Adabi *et al.,* 2006a; Peebles *et al.,* 2007) and improves embryo yolk lipid mobilisation (Peebles *et al.,* 2007). Thus, the presence of L-carnitine in the fertile egg may decrease embryonic mortality by reducing oxidative stress during the hatch process, thereby increasing hatch rate.

In recent years there has been a tendency to utilise *in ovo* injections of L-carnitine into embryonated eggs. In single comb White Leghorns, when L-carnitine was injected *in ovo* in a 0.05 to 10 µmol/egg dose range on d 17 or 18 of incubation, it was shown to have no effect on hatchability, yolk sac weight, or body weight (Zhai *et al.*, 2008a). Nevertheless, bearing in mind its physiological benefits and the lack of any evidence for its toxicity in poultry, when injected in doses up to 10 µmol/egg, Zhai *et al.* (2008a) considered L-carnitine as a potential candidate for improving hatchability and grow-out performance of commercial layers when injected *in ovo* at concentrations higher than 10 µmol/egg (Keralapurath *et al.*, 2010b). Effects of *in ovo* injection of L-carnitine on body weight and the moisture and nutrient biochemical concentrations of various organs and muscles of Ross × Ross 308 broiler chicks, hatched from eggs laid by a 28-wk-old breeder flock, were determined through to 48 d post-hatch. Eggs containing live embryos were injected with L-carnitine (0.5, 2.0, or 8.0 mg dissolved in 100 µl of a commercial diluent) into the amnion on d 18 of incubation using an automated egg injector. The authors concluded that *in ovo* injection of hatching eggs with L-carnitine may decrease liver glucose and increase pipping muscle moisture concentrations of chicks on d 0 and d 3 posthatch (Keralapurath *et al.*, 2010a). Another study by Keralapurath *et al.* (2010b) showed that, although *in ovo* injection did not significantly influence broiler grow-out performance or slaughter yield, L-carnitine has the potential for significantly ($p<0.05$) increasing incubation length and hatchability of broiler hatching eggs.

Levels of usage

Since L-carnitine is a relatively expensive feed supplement, the economic aspect and cost effectiveness must be considered if it is to be routinely applied in certain poultry applications. L-carnitine is available in some countries as an oral preparation of a commercialised form. From a scientific standpoint, L-carnitine can be used in broiler and laying hen diets, at inclusion levels up to 50-200 mg/kg, to support its positive effects (Lettner *et al.,* 1992; Rabie *et al.,* 1997b; Rabie and Szilagyi, 1998; Rodehutscord *et al.,* 2002; Xu *et al.,* 2003; Golzar Adabi *et al.,* 2006a,b; Geng *et al.,* 2007; Nouboukpo *et al.*, 2010). In order to increase semen quality and quantity some studies on breeder flocks has been done with 500 mg/kg L-carnitine (Neuman *et al.,* 2002; Golzar adabi *et al.,* 2007), although some experiments (Zhai *et al.,* 2007) suggest that long-term dietary treatment with 125 mg/kg L-carnitine is enough to obtain positive effects on sperm production.

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Future directions and implications

The use of L-carnitine as an immuno-modulator needs further investigation of other immunological variables in order to establish a basis for possible practical applications; *e.g.* response potential of L-carnitine should be investigated following *in ovo* injection. Nutritional research has recently emphasised the role of nutrients on gene expression and on its regulation (Siddique *et al.,* 2009). Using new genomic technologies such as nutrigenomics, proteomics, transcriptomics and metabolomics, it may be possible to investigate the nutritional modulation of the L-carnitine and elucidate the biological effects of this supplement on cell function and gene expression simultaneously.

It may be useful to test whether the L-carnitine content of broiler feed affects the lysine and methionine requirement of the fast growing chicken. Investigate the bioavailability and the rate of absorption of L-carnitine supplements and their effects on the L-carnitine status of poultry in different ages and evaluate of absorption site and dose dependency.

L-carnitine synthesis and homeostasis in broilers and layers has not yet been studied. It seems that determination of the activity of γ-butyrobetaine dioxygenase, the enzyme which catalyses the last step of L-carnitine biosynthesis and concentrations of precursors for L-carnitine synthesis, trimethyllysine and γ-butyrobetaine will be a useful assessment of whether dietary L-carnitine supplementation could have an effect on L-carnitine biosynthesis. Future studies are required to explore dosimetric effects of L-carnitine supplementation in reproductive performance.

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Table 1 Summary of nutritional effects of L-carnitine in poultry*.

Reference	Poultry species	L-carnitine level (mg kg^{-1})	L-carnitine effects
Performance, Carcass Quality, Serum Parameters			
Cartwright, 1986	Broiler	500	No significant effect performance
Barker and Sell, 1994	Broiler and turkey	0, 50 or 100	No significant effect on performance
Leibetseder, 1995	Broiler	0 and 200	No significant effect on performance and abdominal fat reduction
Rabie *et al.*, 1997c	Laying hen	0, 50 and 500	No significant effect on egg production rate, mean egg weight, daily feed intake, daily egg mass and feed conversion; Albumen quality ↑
Rabie and Szilagyi, 1998	Broiler	0 and 50	Significantly improved growth performance; Breast yield and thigh meat yield ↑; Abdominal fat ↓
Buyse *et al.*, 2001	Broiler	0 and 100	No significant effect on performance; Abdominal fat ↓
Lien and Horng, 2001	Broiler	0 and 160	No significant effect on performance
Daskiran and Teeter, 2001	Broiler	0, 40, 80, 120, 160, and 200	No significant effect on performance; Mortality ↓
Rodehutscord *et al.*, 2002	Broiler	0 and 80	Significantly improved growth and feed conversion
Kita *et al.*, 2002	Broiler	0, 200, 500 and 1000	Significantly improved body weight gain; Plasma insulin-like growth factor-I ↑
Arslan *et al.*, 2003	Duck	0 and 200 via drinking water	No significant effect on performance, carcass traits, serum cholesterol, total lipid, triglyceride and glucose levels
Arslan *et al.*, 2004a	Japanese quail	0 and 100 via drinking water	No significant effect on performance, carcass traits, serum cholesterol, total lipid, triglycerid, total protein and albumin levels; Serum glucose level ↑
Arslan *et al.*, 2004b	Gosling	0 and 100 via drinking water	No significant effect on live weight gain or feed consumption, carcass traits, serum cholesterol, total lipid, triglycerid and glucose; Feed conversion efficiency ↓; Abdominal fat ΣSFA ↑; Abdominal fat ΣPUFA ↓
Cevik and Ceylan, 2005	Broiler	0, 50, 100 and 150	No significant effect on performance but feed conversion ratio at starter period ↓
Kita *et al.*, 2005	Laying hen	0, 25, 50 and 200	No significant effect on egg weight; Albumen height and Haugh unit ↑
Kidd *et al.*, 2005	Broiler breeder	0 and 25	No significant effect on progeny performance; Progrny abdominal fat ↓
Golzar Adabi *et al.*, 2006a	Broiler breeder	0 and 60 for female; 0 and 500 male	No significant effect on internal and external egg quality; Total egg production ↑; Egg yolk cholesterol ↓; Egg yolk L-carnitine concentration ↑
Deng *et al.*, 2006	Laying hen	0, 100 and 1000	No significant effect on growth rates, feed intake or feed utilisation efficiency
Sarica *et al.*, 2007	Japanese quail	0 and 50	No significant effect on performance; Shelflife stability of meat ↑
Buyse *et al.*, 2007	Broiler	15 and 100	No significant effect on performance
Zhai *et al.*, 2008b	Layer breeder	0 and 125	No significant effect on hatch rate, egg production, and egg traits; Egg yolk L-carnitine concentration ↑
Hajibabaei *et al.*, 2008	Ostriches	0, 250 and 500	Egg production ↑
Suchy *et al.*, 2008	Pheasant	0 and 100	Egg production and weight ↑
Kidd *et al.*, 2009	Broiler	0, 10, 20 ,30, 40 and 50	No significant effect on performance; Dark meat yield ↑ in 40 mg/kg supplemented group
Keralapurath *et al.*, 2010a	In-ovo injected	0.5, 2.0, and 8.0 mg dissolved in 100 μL of a	Liver glucose ↓ pipping muscle moisture concentrations ↑ on d 0 and 3 posthatch respectively

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Table 1 Continued

Reference	Poultry species	L-carnitine level (mg kg^{-1})	L-carnitine effects
		commercial diluent	
Ghods-Alavi *et al.*, 2010	Laying hen	0, 50, 100 and 150	Egg yolk cholesterol and triglycerides ↓; Abdominal fat ↓; Albumen height ↑
Immunity			
Mast *et al.,* 2000	Broiler	0 and 100	Total Ig (Ig) (but not IgM)and IgG ↑
Janssens *et al.,* 2000b	Pigeons	0 and 1000 via drinking water	Primary bovine serum albumin specific IgG and IgM ↑
Deng *et al.*, 2006	Laying hen	0, 100 and 1000	Thymus weight ↑; Serum primary antibody response to sheep red blood cells (SRBC) ↑
Golzar Adabi *et al.*, 2006b	Broiler	0, 25, 75 and 100	Serum primary antibody response to sheep red blood cells (SRBC) ↑; anti Newcastle virus (NDV) antibody ↑; bursa of Fabricius, spleen and thymus weight ↑
Buyse *et al.*, 2007	Broiler	15 and 100	Blood hemopexin and alpha-1 acid glycoprotein ↑; innate immune response ↑
Reproduction			
Leibetseder, 1995	Broiler breeder	50 and 100	Hatchability ↑; Egg yolk L-carnitine concentration ↑
Neuman *et al.,* 2002	Layer breeder	0 and 500	Sperm concentration ↑; Testicular multinucleated giant cells ↓;
Thiemel and Jelinek, 2004	Broiler breeder	0 and 30	Hatchability ↑; Unfertilized eggs ↓; Blood glucose and magnesium ↑; Total protein, cholesterol, calcium and phosphorus ↓
Peebles *et al.,* 2007	Broiler breeder	0 and 25	No significant effects on embryonic mortalities, hatchability; Egg yolk L-carnitine concentration ↑; Ovarian follicle yolk deposition ↑
Zhai *et al.*, 2007	Layer breeder	0, 125, 250 and 500	No significant effects on semen viability and semen volume; Sperm concentration ↑
Golzar Adabi *et al.,* 2007	Broiler breeder	0 and 60 for female; 0 and 500 male	Semen volume, sperm motility, sperm viability, sperm count↑; Hatchability ↑
Golzar Adabi *et al.,* 2008	Ostriches	0, 250 and 500 ppm	No significant effects on abnormal sperm; Semen volume, sperm motility, live sperm percent, sperm count↑
Zhai *et al.*, 2008b	Layer breeder	0 or 125	Sperm concentration ↑

Unit of L-carnitine is based on mg/kg otherwise it has been noted in table
ΣSFA = total saturated fatty acid; ΣPUFA = total polyunsaturated fatty acid